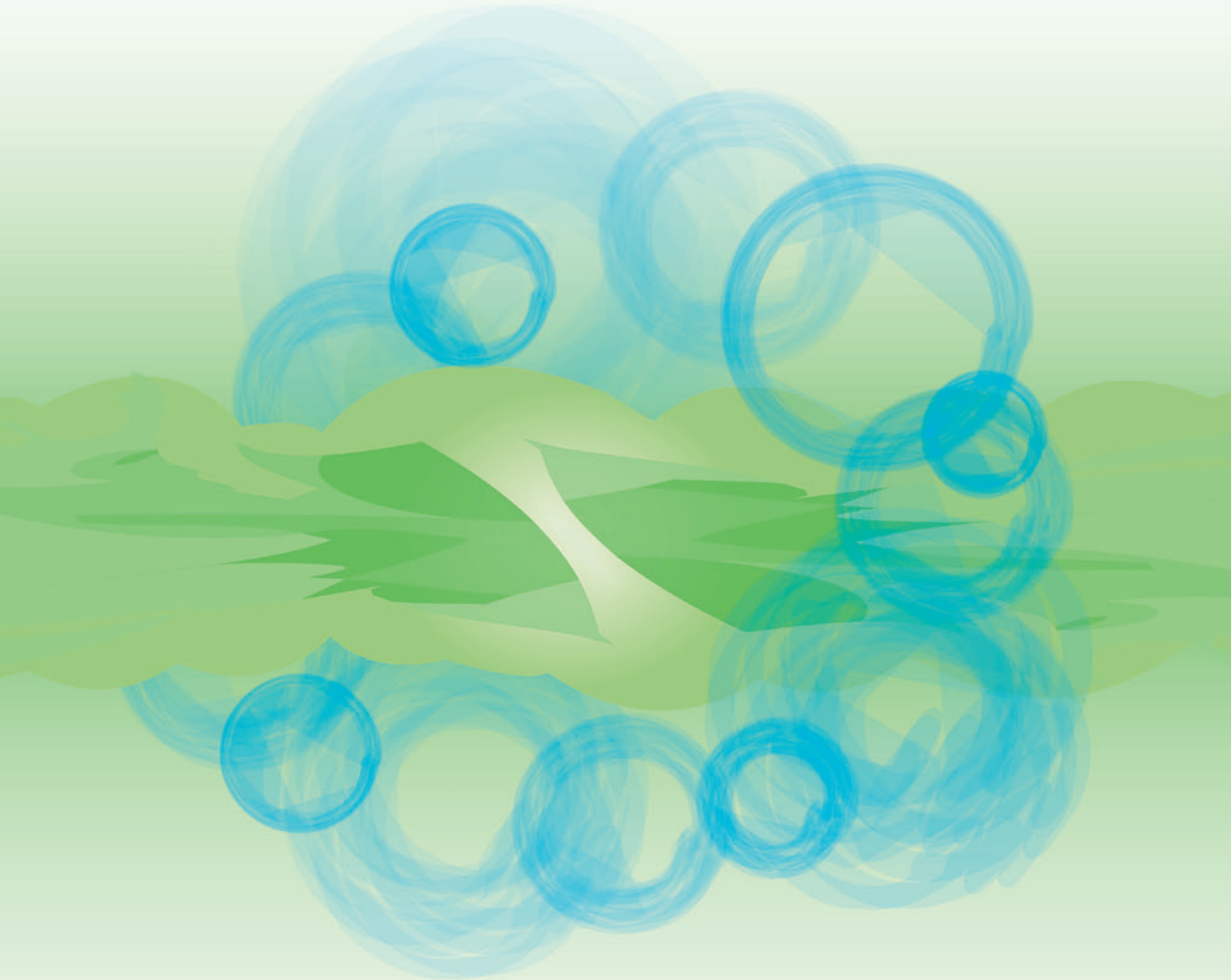
Optimization of peri-operative care in colorectal surgery



Verena N.N. Kornmann

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Verena Kornmann

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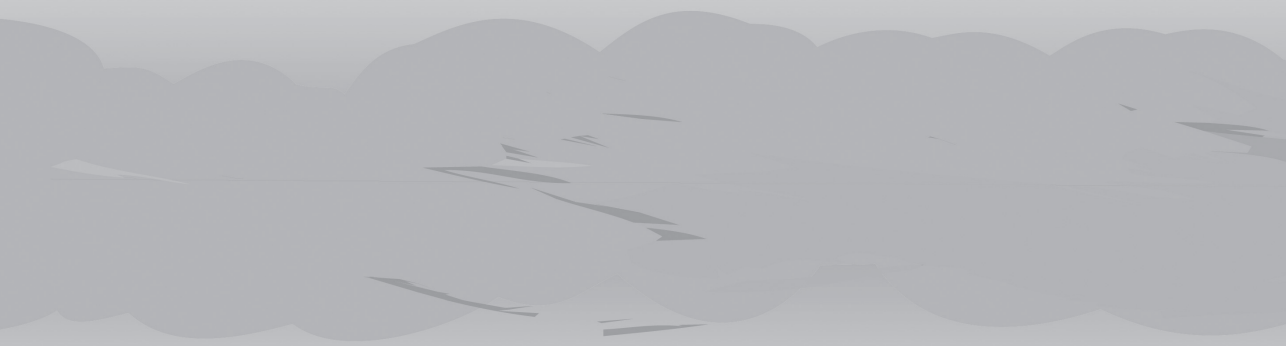
CONTENTS

Part 4 - Functional outcome and quality of life after colorectal surgery



Chapter 1

General introduction and outline of the thesis

INTRODUCTION

Colorectal cancer is an important health issue with worldwide 1.36 million new cases and 694.000 deaths a year.[1] The incidence in the Netherlands was 15.000 in 2014 and this is still increasing.[2,3] It is the second most common cancer in men after prostate cancer, and the third most common cancer in women after breast and skin cancer.[2,3] Colorectal surgery is the cornerstone in the treatment of colorectal cancer, with or without (neo-)adjuvant treatment. With aging of the population, surgery is increasingly being performed in elderly patients.[4] In addition, an increased use of surgical treatment is also seen in benign colorectal diseases, such as diverticulitis and inflammatory bowel disease.[5,6]

Complications following colorectal surgery

Despite increasing experience which has been gained in technical aspects of surgery and peri-operative care, complications after colorectal surgery are unavoidable. Since the introduction of a grading system of surgical complications by Clavien and updated by Dindo in 2004, complications after colorectal surgery have extensively been evaluated.[7-9] The Dutch Surgical Colorectal Audit (DSCA), a disease specific national audit in which surgically treated colorectal cancer patients are registered, calculated a complication rate of 30% after colonic surgery and 37% after rectal cancer surgery in 2014.[10] Mortality rates were 2.7% and 1.1%, respectively.

Anastomotic leakage following colorectal surgery

Anastomotic leakage is a severe complication following colorectal surgery. The Dutch Surgical Colorectal Audit reported a leakage rate of 5.9% following colonic surgery, and 9.3% following rectal surgery in 2014.[10] Although there is a trend to decreasing leakage rates during the recent years, leakage still occurs. In the general literature, leakage rates of less than 1% up to more than 20% have been described.[11] Mortality, associated with anastomotic leakage, is considerably. One of the main limitations in comparing literature on the outcome of anastomotic leakage, is the wide variety of terminology used to define clinical and radiologically anastomotic leakage. In 1991, a standardized definition for anastomotic leakage was proposed by the UK Surgical Infection Study Group.[12] However, in 2001, a total of 29 different definitions for anastomotic leakage of the lower gastrointestinal tract were identified by Bruce and co-workers.[13] The definition of anastomotic leakage used in this thesis includes: anastomotic dehiscence visualized at relaparotomy or endoscopy, or percutaneous/ transanal drainage of pus/ enteral contents adjacent to the anastomosis. A radiological anastomotic leak was defined as the presence of extraluminal contrast medium, air bubbles adjacent to the anastomosis or perianastomotic fluid collections with or without pneumoperitoneum.

Risk factors for postoperative complications

General risks of colorectal surgery are comparable with those of any abdominal surgical procedure, but the extent of risk may vary among different resections. Moreover, patient specific risk factors may increase the risk for postoperative complications. Some risk factors may be influencable, whereas others are non-influencable factors.[14,15] Multiple risk scores have been developed to stratify patients' surgical risks, such as the American Society of Anesthesiologists classification, Charlson Comorbidity Index, and others.[16-21] These risk scores aim to predict a complicated postoperative course in general and do not specify which particular complication might occur in what specific patient. The patient with all its characteristics and risk factors would guide us to an individual "risk passport", predicting which complications may occur postoperatively.[22] As we are currently individualizing perioperative cancer care, in terms of treatment strategy, it is also important to try to individualize perioperative patient management in terms of anticipation and prevention, i.e. early diagnosing and management of postoperative complications, which is already to be expected to occur.

Failure to rescue

Over the years, several new technical innovations, i.e. laparoscopic surgery instead of traditional open procedures, and new protocols, i.e. enhanced recovery after surgery (ERAS) and international healthcare safety programs, have been introduced to improve the quality and safety of care and to reduce postoperative morbidity and mortality.[23-28] If postoperative complications occur, early detection is of utmost importance to diminish the impact of complications, but may be challenging.[29] Furthermore, the effectiveness of the management of critically ill patients has been improved. Suboptimal care has led to preventable adverse events and even in-hospital mortality.[30-32] The results of the DSCA demonstrated a significant variability in failure-to-rescue rates among different hospitals.[33,34] Even the role of the nurse-staffing levels and patients outcome has been discussed.[35] A large study, covering 1.104.659 discharges of surgical patients, demonstrated a lower failure-to-rescue rate with an increased number of hours of care per day by registered nurses.[36] In response to these findings, trigger systems, i.e. the 'early warning score' (ESW) and medical emergency teams, have been introduced worldwide to allow early identification of patients with deteriorating clinical conditions.[37-42]

THESIS OUTLINE

This thesis aims to improve knowledge on patient-related and intra-operative risk factors for postoperative complications following colorectal surgery, the diagnostic accuracy if complications occur and the impact on quality of life after colorectal surgery.

In ***Chapter 2***, we present the technique in which a fully intracorporeal anastomosis is performed during laparoscopic right hemicolectomy with the advantage of no externalization of vital bowel, optimization of cosmetics and improvement of patient satisfaction.

With aging of the population, colorectal cancer surgery in the elderly is increasingly being performed, but treatment in these patients is challenging. In ***Chapter 3***, the influence of postoperative complications on the outcome in the first year after surgery is investigated.

Adequate tissue perfusion and oxygenation is of importance in healing of the anastomosis. A compromised local vascular supply following colonic resection may increase the risk of ischemia and impaired anastomotic healing, resulting in anastomotic leakage. The aim of ***Chapter 4*** was to find any relation between radiologically visible atherosclerosis and anastomotic leakage. In ***Chapter 5*** the microcirculation of the human bowel is visualized for the first time during surgery by using SDF imaging.

Early detection of anastomotic leakage after colorectal surgery is of importance to reduce morbidity and mortality. In ***Chapter 6***, the literature is reviewed on the value of abdominal CT-scanning in the detection of anastomotic leakage. The sensitivity, but also the consequences of a false negative CT-scans are demonstrated in ***Chapter 7***.

To adequately respond on postoperative complications, especially anastomotic leakage, following colorectal surgery, an optimal clinical diagnostic strategy is necessary. In ***Chapter 8***, a study protocol of the multicenter CONDOR-study (Early COmplication Detection after colORectal surgery) is presented.

In ***Chapter 9 and 10***, we investigated the quality of life in terms of fecal incontinence following rectal cancer surgery and its risk factors in the general population and in elderly.

Finally, in ***Chapter 11 and 12*** we summarize and discuss the main findings of this thesis.

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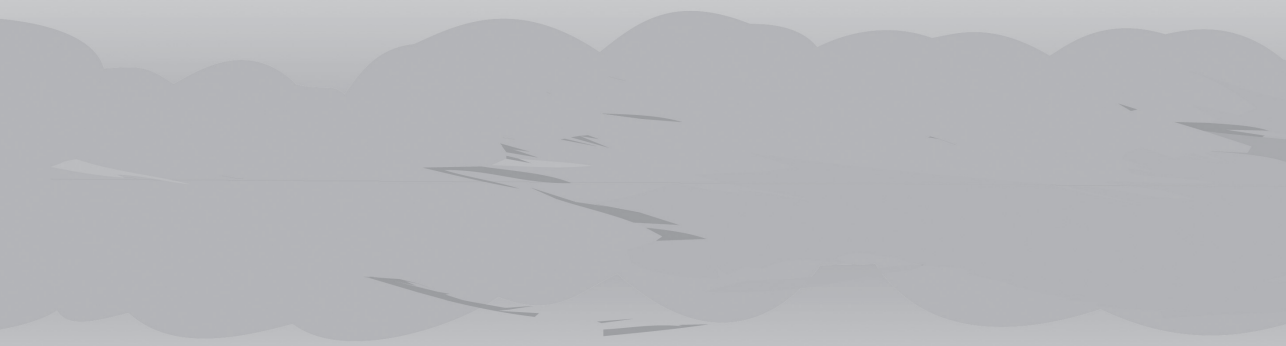
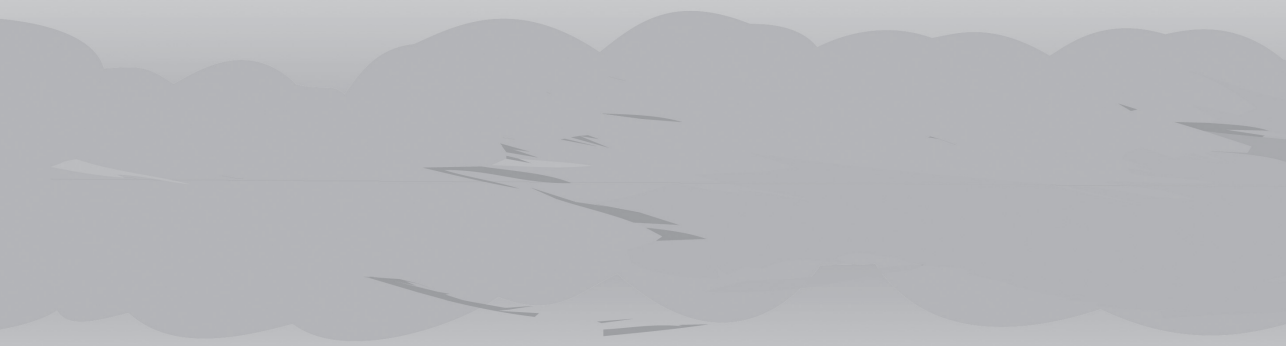


PART I

Risk factor and complications after colorectal surgery



Chapter 2

Totally laparoscopic right hemicolectomy with intracorporeal anastomosis is a technically and oncologically safe procedure

Verena Kornmann, Jeroen Hagendoorn, Sebastiaan van Koeverden,
Bert van Ramshorst, Anke Smits

Acta Chirurgica Belgica, 2013, 113, 439-443

ABSTRACT

Background

During laparoscopic right hemicolectomy, most surgeons perform an extracorporeal anastomosis. A totally laparoscopic procedure with intracorporeal anastomosis may improve cosmesis because midline- or para-umbilical incisions can be avoided. Here, we investigate the safety of an intracorporeal anastomosis from a technical and oncological perspective.

Methods

All patients who underwent right hemicolectomy with intracorporeal anastomosis between 2003-2011 were retrospectively analyzed. Parameters were duration of surgery, intraoperative blood loss, mortality and morbidity. Adequacy of oncologic resections was scored by resectional margins and number of harvested lymph nodes.

Results

A total of 162 patients were included with a median age of 69 years (IQR60-76). The duration of surgery was 100 minutes (80-120) and intraoperative blood loss was 30 mL (10-100). Hundred-twenty patients (74%) underwent an oncologic resection. Number of harvested lymph nodes was 12 (9-18). R0-resection was achieved in 100%. Four patients died (2.5%). Postoperative complications were: anastomotic leakage (3.1%;n=5), ileus (4.9%; n=8), abscesses (2.5%; n=4), wound infection (3.1%; n=5) and cardiopulmonary complications (10.5%; n=17). Duration of oncological follow-up was 2.5 years (1.3-4.6). Local recurrence and overall survival rates at two years were 0.8% and 85.4%, respectively.

Conclusion

Right hemicolectomy with intracorporeal anastomosis is a technically and oncologically safe procedure with acceptable operating time and low mortality.

INTRODUCTION

Open and laparoscopic colectomy are two techniques applied for the resection of right sided colonic tumors. Previous studies have shown the benefits of laparoscopic surgery, despite the technically more demanding procedure. Advantages of laparoscopic surgery include diminished blood loss, less postoperative pain, less complications, quicker recovery and shorter postoperative length of stay at the hospital.[1-5] In most series of laparoscopic right hemicolectomy[1-5], the hemicolon is externalized through a midline- or right paraumbilical incision and the anastomosis is performed extracorporeally. An intracorporeally performed (totally laparoscopic) anastomosis carries the advantage that no externalization of vital bowel with concomitant traction on the mesentery is necessary. Moreover, the extraction site of the resection specimen can be chosen to optimize cosmesis (e.g., a Pfannenstiel incision) and hence patient satisfaction. Surprisingly, there are few data in the literature on the outcome of a complete laparoscopic procedure with intracorporeal anastomosis. Several case-series have described totally laparoscopic right colectomy in adults with excellent morbidity and mortality and clinical results.[6-11] Unfortunately, these studies are hampered by small patient numbers or short clinical follow-up. Thus, there remains a paucity of data on the benefits and oncological safety of laparoscopic right hemicolectomies with intracorporeal anastomosis.

In this study we investigated the safety of a complete laparoscopic procedure in terms of morbidity and mortality in a larger cohort of adult patients with right-sided colonic disease. We hypothesized that right hemicolectomy with intracorporeal anastomosis is a safe and adequate oncological procedure.

MATERIAL AND METHODS

All consecutive adult patients who were eligible for a complete laparoscopic right hemicolectomy with intracorporeal anastomosis for benign or malignant colonic disease at the St. Antonius Hospital, Nieuwegein, the Netherlands, between January 2003 and December 2011 were included in this study. All procedures were performed by two experienced laparoscopic surgeons. Patients in whom preoperatively was decided to perform an open procedure and patients with preoperatively staged T4 colorectal tumors (according to the TNM staging system for colorectal cancer of the American Joint Committee on Cancer (AJCC)) were excluded from this study.[12]

Outcomes were operating time, intraoperative blood loss, postoperative length of stay at the hospital, hospital readmission within 30 days, 30-day or in-hospital mortality, short-term complications which were measured during the first 30 days after surgery using the Common terminology criteria for adverse events (CTCAE)[13] and long-term oncological follow-up. Adequacy of oncologic resections was scored by resectional margins and number of harvested lymph nodes. Preoperative, intraoperative and postoperative data were collected from demographic data and review of clinical records, operative reports and histological data.

Laparoscopic assisted right colectomy was considered when the anastomosis was created extracorporeal. In procedures with conversion to laparotomy unplanned incisions or incisions > 5cm were required and the anastomosis was created extracorporeally.

Surgical technique

Pneumoperitoneum was established via the percutaneous insertion of a Verres needle. After adequate insufflation, a 10-mm umbilical camera port was inserted under visual control. Under direct visualization two to three ports were placed, including a 12-mm working port in the upper left abdomen and one or two 5-mm working ports in the right lower abdomen or supraumbilical region. The abdomen was then inspected for the localization of the tumor or inflammation and any signs of metastatic disease. The right colon and mesentery were mobilized in a medial-to-lateral fashion. After identification of the ileocolic, right colic, and right branch of the middle colic artery and veins, the vessels were divided near their origin. The terminal ileum and transverse colon were divided with an Endo-GIA stapler (Covidien, Dublin, Ireland). During the full laparoscopic procedure, all steps were completed intracorporeally. A side-to-side isoperistaltic anastomosis between the ileum and transverse colon was created by using the Endo-GIA stapler and single-layer Vicryl sutures. In three patients a small incision in the right flank was necessary to mobilize a large tumor. In these patients the anastomosis was created intracorporeally and they were therefore included in the full laparoscopic group. In all but three cases the specimen was extracted through a Pfannenstiel incision.

Statistical analysis

Values are given as number of patients or median with inter quartile range (IQR). The learning curve was expressed as the difference in operating time and intraoperative blood loss between the first half (January 2003- June 2007) and the second half (July 2007- December 2011) of the study and was tested with the Mann-Whitney-U test. Overall survival was calculated with the Kaplan–Meier method. The data was analyzed with SPSS statistical software (SPSS Statistics Version 17.0, Inc., Chicago, Illinois, USA).

RESULTS

Patient and intraoperative characteristics

A total of 181 patients were eligible for inclusion in the study. In 90% (n=162) a full laparoscopic right hemicolectomy with intracorporeal anastomosis was performed. In three patients (2%) a laparoscopic assisted right hemicolectomy was performed and in 16 patients (9%) conversion to laparotomy was required due to a large tumor, multiple adhesions, low visibility or unrecognizable anatomy. Since no intracorporeal anastomosis was created in these 19 patients, they were excluded from further analysis.

The group who underwent full laparoscopic surgery consisted of 67 males (41%) and 95 females (59%) with a median age of 69 years (IQR 60-76). Forty-nine patients (30%) had a history of abdominal surgery for i.e. appendicitis, gallstones, previous abdominal malignancy, gynecological disease, etc. The duration of surgery was 100 minutes (IQR 80-120) and intraoperative blood loss was 30 mL (IQR 10-100). Intraoperative blood loss was significantly reduced during the second half of the study, 25 mL (IQR 10-50) versus 50 mL (IQR 10-200), p=0.001. Baseline characteristics are summarized in table 1.

Table 1. Summarized patient characteristics

	Intracorporeal anastomosis (n = 162)
Sex: male/female (n)	67 (41.4%) / 95 (58.6%)
Age at surgery (years)	69 (60-76)
BMI	25.3 (22.3-30.4)
ASA-classification	2 (2-2)
Previous abdominal surgery (n)	49 (39.5%)
Pathology:	
Benign (n)	42 (25.9%)
Malignant (n)	120 (74.1%)
Duration of surgery (min)	100 (80-120)
First half of study (2003-june2007)	100 (85-125)
Second half of study (july2007-2011)	95 (80-120)
Blood loss (mL)	30 (10-100)
First half of study (2003-june2007)	50 (10-200)
Second half of study (july2007-2011)	25 (10-50)

Values are given as number of patients (% of group) or median (inter quartile range). BMI body mass index, ASA American Society of Anaesthesiologists.

Postoperative characteristics

The median length of hospital stay was 5 days (IQR 4-8). Nine patients (5.6%) were readmitted to the hospital within 30 days, mainly due to intra-abdominal abscesses, ileus and one patient with anastomotic leakage. Postoperative complications were anastomotic leakage confirmed at relaparotomy in 3.1% (n=5), postoperative ileus in 4.9% (n=8), abscess for which surgical or radiologic drainage was required in 2.5% (n=4) and wound infection in 3.1% (n=5). Cardiac complications such as cardiac decompensation and atrial fibrillation were seen in 3.1% (n=5). Pulmonary complications included pulmonary embolism and pneumonia and were observed in 7.4% (n=12). Four patients (2.5%), all with an ASA-score of 3, died postoperatively, of which 3 patients during the first half and one patient during the second half of the study. Two patients underwent relaparotomy because of intra-abdominal abscesses and anastomotic leakage and died after respiratory insufficiency due to pneumonia or pulmonary embolism on day 19 and 30, respectively. One patient underwent relaparotomy due to small bowel perforation and postoperative course was further complicated by pulmonary embolism and pericardial effusion, which resulted in death on day 65. The fourth patient with pre-existent pulmonary and cardiac comorbidity died on day 7 after multiple organ failure. The postoperative data and complications are shown in table 2.

Table 2. Postoperative characteristics

	All patients (n = 162)
Length of stay at the hospital (days)	5 (4-8)
Readmission < 30 days (n)	9 (5.6%)
Mortality (n)	4 (2.5%)
Complications (n)	
Anastomotic leakage	5 (3.1%)
Ileus	8 (4.9%)
Abscess	4 (2.5%)
Wound infection	5 (3.1%)
Cardiac complication	5 (3.1%)
Pulmonary complication	12 (7.4%)

Values are given as number of patients (% of group) or median (inter quartile range).

Pathologic results and oncologic outcomes

Histopathology revealed benign disease in 26% (n=42), including diverticulitis, Crohn's disease or benign tumours. Hundred-twenty patients (74%) underwent resection for malignant disease. Results are depicted in table 3. A R0-resection was achieved in 100% of the patients with malignant disease. The median number of harvested lymph nodes was 12

Table 3. Oncologic resections

	Malignant disease (n = 120)
TNM Stage I	32 (26.7%)
Stage II	48 (40.0%)
Stage III	40 (33.3%)
T- stage	
Stage T1	7 (5.8%)
Stage T2	29 (24.2%)
Stage T3	63 (52.5%)
Stage T4 or metastasis	21 (17.5%)
N-stage	
Stage N0	80 (66.7%)
Stage N1	28 (23.3%)
Stage N2	12 (10.0%)
Lymph nodes	12 (9-18)
Tumorpositive lymph nodes	0 (0-1)
R0-resection	120 (100%)
Follow-up	
Mean duration of follow-up (years)	2.5 (1.3-4.6)
Local recurrence at 2 years	1 (0.8%)
Metastatic disease after 1 year of follow-up	14 (11.7%)

Values are given as number of patients (% of group) or median (IQR). T1-4 according to the TNM-classification.

(IQR 9-18). In 88 patients (73%) more than 10 lymph nodes were harvested. Median duration of oncological follow-up was 2.5 years (IQR 1.3-4.6 years), with a maximum follow-up of 9.2 years. Of these patients, 96.7% were followed for at least one year, 68.3% for at least two years, 57.5% for at least three years and 42.5% for at least five years. The rate of local recurrence at two years was 0.8%. The overall survival rate at two years was 85.4% for all stages (figure 1), 78.9% for stage I, 94.1% for stage II and 79.3% for stage III (figure 2).

DISCUSSION

In our study, we investigated the safety and outcome of patients who underwent laparoscopic right hemicolectomy with intracorporeal anastomosis in a period of 9 years. A total of 181 patients were included in this study of which 162 patients underwent full laparoscopic surgery. To our knowledge, larger patient series with an intracorporeal anastomosis in right hemicolectomy have not been described. We have found in this study

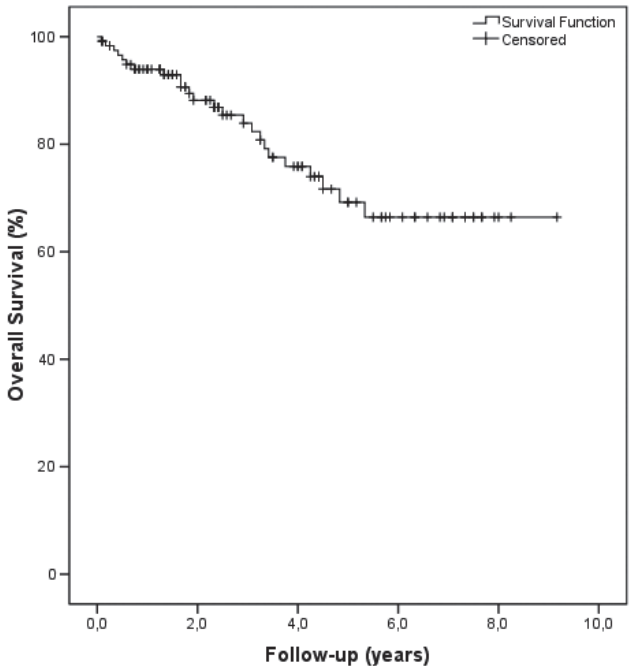


Figure 1. Overall survival according to all TNM stages.

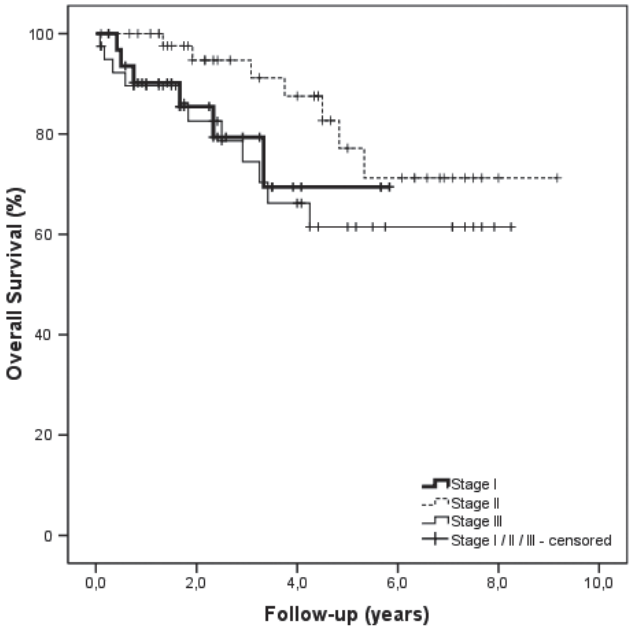


Figure 2. Overall survival according to TNM stage I, II or III.

that complete laparoscopic right hemicolectomy with intracorporeal anastomosis is an oncologically safe procedure in which R0-resection was achieved in 100% of the patients with a median number of 12 harvested lymph nodes.

The benefits of laparoscopic surgery compared with open procedures have extensively been described in the literature.[1-5,14,15] Minimally invasive surgical procedures with an extracorporeal anastomosis are increasingly accepted in the treatment of right sided colonic disease. However, a small number of previous studies have suggested the potential benefits and short-term clinical safety of intracorporeal anastomosis compared with laparoscopic assisted or open procedures.[6-10] Our results are in accordance with these data, with a median duration of surgery for the group with intracorporeal anastomosis of 100 minutes and minimal intraoperative blood loss, which was improved during the second half of the study. The postoperative length of stay observed in this study was consistent with previous described studies. The limited data of studies comparing intracorporeal versus extracorporeal anastomosis show that the length of hospital admission is not affected by the type of anastomosis.[7-8] Anastomotic leakage was seen in 5 patients (3.1%) with full laparoscopic surgery. This incidence is slightly higher compared with previous studies on relatively small numbers.[7-10] All of these patients were classified ASA score 2 or 3, two patients had a history of abdominal surgery and two other patients were operated for Crohn's disease. Four patients with pre-existent comorbidity died in our study, all due to postoperative major complications. In addition, there was a reduction of postoperative complications in the second half of the study compared with the first half.

Several studies comparing open versus laparoscopic right hemicolectomy for colon cancer have shown that laparoscopic surgery is an oncologically safe procedure with no significant differences in the number of removed lymph nodes or tumor-free resection margins.[16-17] Nakamura et al described in a retrospective case-control study that the recurrence rate and disease free survival were not significantly different between open and laparoscopic oncological resections.[16] In our study R0-resection was achieved in 100%. The number of harvested lymph nodes and overall survival is in the range with the literature.[7,10,18] Therefore we can conclude that the full laparoscopic right hemicolectomy is an adequate safe oncological procedure. The overall survival rate at two years was lower for stage I (78.9%) compared to stage II (94.1%). This may be explained by small patient groups and a higher ASA score with more comorbidity in patients with stage I. Mortality during the first two years after surgery in this group was mostly the result of non-cancer related causes.

One of the advantages of performing an intracorporeal anastomosis is that midline- or paraumbilical incision can be avoided since the extraction site of the resection specimen can be chosen, which improves cosmesis. In our study the extraction site of the specimen was preferably via a Pfannenstiel incision. Scatizzi et al described in a recent case-control study a significantly improved cosmesis and patient comfort in favor of the intracorporeal anastomosis.[8] A study by Hellan including 80 patients who underwent right hemicolectomy (23 patients with intracorporeal and 57 patients with extracorporeal anastomosis) demonstrated similar complication rates for both groups with significant shorter incision length (p=0.004) in the group with intracorporeal anastomosis.[7]

CONCLUSION

In conclusion, our data suggest that a full laparoscopic right hemicolectomy with intracorporeal anastomosis performed by experienced surgeons is a technically safe and oncologically adequate procedure.

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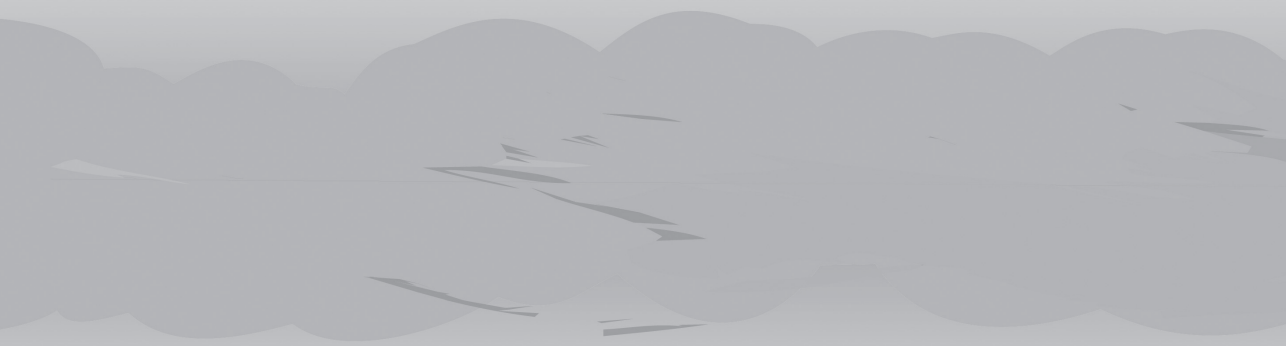

Chapter 3

The first year after colorectal surgery in the elderly

Verena Kornmann, Jeroen van Vugt, Anke Smits, Bert van Ramshorst, Djamila Boerma

Submitted

ABSTRACT

Background

Surgery for colorectal malignancy is increasingly being performed in the elderly. Little is known about the impact of complications on late mortality. The aim of this study was to analyze whether a complicated postoperative course affects the one-year survival in the elderly patient.

Methods

All consecutive patients older than 75 years of age undergoing colorectal cancer surgery between January 2009 and April 2013 were included in this study. The main outcome was mortality at one year after surgery. Logistic regression analyses were performed to determine risk factors for a poor outcome (mortality) after survival of the early postoperative course of surgery at one year follow-up. Patients who deceased within 30 days postoperatively, were excluded from analysis.

Results

The early mortality rate was 6.3% (n=15) and two patients died during follow-up as a result of complications after second surgery. A total of 223 patients survived the perioperative period and were included in this study. Twenty-two patients (9.9%) died during the first year of follow-up. Stage IV disease (OR 5.716 (95% CI 1.82-17.642), p=0.002), complications of primary surgery (OR 4.112 (1.308-12.930), p=0.016) and comorbidity (OR 2.453 (1.002-6.008), p=0.050) and were risk factors for one-year mortality. ICU-stay, reoperations and readmissions were not associated with a worse one-year outcome.

Conclusion

Elderly patients with stage IV disease at time of surgery, comorbidity, and postoperative complications are at risk for mortality during the first year after surgery. A patient-tailored approach with special attention for perioperative care should be considered in the elderly.

INTRODUCTION

With aging of the population, colorectal surgery for cancer in older patients is increasingly being performed.[1] The surgical treatment of elderly with colorectal malignancies is challenging.[2] Two systematic reviews report lower overall survival rates compared with younger patients.[3,4] Understandably, the highest mortality rate in elderly occurs in the early postoperative period[5,6], but cancer-related survival is equal in older and younger patients when patients survive the first year after colorectal surgery.[5,7] Little is known about the survival and readmission rate s during the first year after surgery, and whether this out-patient course is determined by the early postoperative in-hospital course. The aim of this study was to evaluate the course after the postoperative period, and to investigate the influence of the early postoperative course on the outcome after one year. This knowledge may allow a patient-tailored approach and shared-decision making during hospital admission if complications of surgery may occur.

MATERIALS AND METHODS

Population and data acquisition

Patients aged 75 years or older who underwent colorectal cancer surgery at the St Antonius Hospital, Nieuwegein, the Netherlands, between January 2009 and April 2013 were enrolled in a retrospective database. Data on the postoperative course, including postoperative complications (i.e. surgical and non-surgical complications within 30 days after surgery, during admission or during readmission within 30 days), early mortality (mortality within 30 days postoperatively or in-hospital) and mortality during follow-up (within one year following surgery), reoperations, ICU stay and readmissions, were evaluated. Comorbidity was categorized using the American Society of Anesthesiologists (ASA) classification and the Charlson Comorbidity Index.[8,9] The Common Terminology Criteria for Adverse Events (CTCAE) were used to define postoperative complications[10] and the Clavien-Dindo Classification of Surgical Complications was used to classify the severity of complications.[11-13]

Statistical analysis

Data are presented as number of patients with percentage or as median with inter quartile range (IQR). To determine variables contributing to a worse one-year outcome in 'survivors of the surgery', patients who died during the first 30 days or in-hospital (early mortality) were left out the analysis. Differences between groups were tested with the Chi-square test (for binomial outcomes). Logistic regression analysis (enter method) was

used to determine independent risk factors for one year mortality in survivors of surgery, including all variables with a p-value inferior to 0.050 in univariate analysis. A p-value ≤ 0.05 (two-tailed) was considered significant. Data were analysed using SPSS version 21.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 256 patients were included. Of these patients, follow-up was incomplete in 16 (6.3%) patients. These patients were excluded from analysis. The early mortality rate was 6.3% (n=15) as a results of surgical (n=5) and non-surgical (n=10) postoperative complications. A total of 225 survived the early postoperative period after colorectal surgery. Two patients died during follow-up due to complications after a second surgical procedure (one stoma reversal and one adhesiolysis with partial small bowel resection for ileus). The remaining 223 patients were included in the analysis: 113 males (50.7%) and 110 females (49.3%) with a median age of 79 years (IQR 76-83). Baseline and postoperative characteristics are summarized in table1.

Mortality rates

During the first year after surgery, 22 of the 223 included patients (9.9%) died due to progressive cardiopulmonary morbidity (n=8), secondary (lung) cancer (n=1) or cancer status (n=13). After one year, 201 of the 223 patients (90.1%) were still alive.

Postoperative course

Postoperative morbidity

Postoperative complications after initial colorectal surgery occurred in 103 patients (46.2%) and were mostly graded as Clavien-Dindo score 1-2 (table 1). Thirty-eight patients needed re-operation due to complications (Clavien-Dindo 3-4). The occurrence of postoperative complications was associated with death during the first year of follow-up. Of patients with postoperative complications, 68.2% (n=15) died after discharge during the first year, versus 31.8% of the patients who died and had not suffered from complications (n=7), p=0.041. The grade of the complications (Clavien-Dindo score ≥ 3) did not influence the risk of death after discharge, nor did the need for re-operation, p=0.498 and p=0.457, respectively (table 2).

ICU-stay

A total of 13 patients (5.8%) were admitted to the ICU for less than five days as a result of postoperative complications and 10 patients (4.5%) required more than five days of ICU

Table 1. Baseline and peri-operative characteristics

	All patients ≥ 75 years (n = 223)
Age (years)	79 (76-83)
Sex (female)	110 (49.3%)
BMI (kg/m^2)	25.1 (23.0-27.5)
Charlson Comorbidity Index	3 (2-4)
ASA classification	2 (2-3)
Surgical procedure (n)	
- Right-sided colectomy	93 (41.7%)
- Left-sided colectomy	75 (33.6%)
- Rectal resection	51 (22.7%)
- (Sub)total colectomy	4 (1.8%)
Emergency surgery (n)	29 (13.0%)
Approach (n)	
- Laparotomy	105 (47.1%)
- Laparoscopic	104 (46.6%)
- Converted	14 (6.3%)
Stomy / anastomosis (n)	
- Anastomosis	137 (61.4%)
- No stomy	130 (58.3%)
- Diverting stomy	6 (2.7%)
Duration of surgery (min)	100 (75-135)
Blood loss (ml)	50 (25-100)
pTNM classification	
- pT	2 (2-3)
- pN	0 (0-1)
- Stage IV (n=195)	29 (13.0%)
Length of stay at the hospital (days)	7 (5-12)
Stay at ICU	
- 24-hour observation (n)	16 (7.2%)
- Length of stay at ICU (< 5 days (n)	13 (5.8%)
- Length of stay at ICU (≥ 5 days (n)	10 (4.5%)
Readmission to the hospital (n)	30 (13.5%)
Complications (n)	103 (46.2%)
- Clavien Dindo Score 1-2 (n)	64 (28.7%)
- Clavien Dindo Score 3-4 (n)	39 (17.5%)
Reoperation / reintervention (n)	38 (17.0%)

Values are expressed as numbers (percentage) or median with inter quartile range. BMI, Body Mass Index; ASA, American Society of Anesthesiologists; ICU, Intensive Care Unit.

care (table 2). ICU stay (short nor long) was not associated with mortality during follow-up (p=0.988).

Table 2. Univariate logistic regression analysis (n=223)

	OR (95% CI)	p-value
Patient characteristics		
Age (years)	1.074 (0.969-1.1190)	0.174
Sex (male)	2.252 (0.881-5.759)	0.090
BMI (kg/m^2)	0.909 (0.796-1.039)	0.163
Charlson Comorbidity Index	1.331 (1.062-1.669)	**0.013**
ASA classification	2.782 (1.320-5.863)	**0.007**
Intra-operative characteristics		
Surgical procedure (n)		
- Right-sided colectomy	1.000 (ref.)	0.729
- Left-sided colectomy	1.132 (0.435-2.947)	0.800
- Rectal resection	0.519 (0.136-1.978)	0.366
- (Sub)total colectomy	0.000 (0.000-0.001)	0.999
Emergency surgery (n)	1.564(0.490-4.998)	0.450
Approach (n)		
- Laparotomy	1.000 (ref.)	0.344
- Laparoscopic	0.511 (0.195-1.337)	0.171
- Converted	1.179 (0.237-5.875)	0.840
Stomy / anastomosis (n)		
- Anastomosis	0.730(0.301-1.770)	0.486
- No stomy	1.451 (0.601-3.505)	0.408
Duration of surgery (min)	0.994 (0.982-1.006)	0.327
Blood loss (ml)	0.999 (0.996-1.002)	0.728
Pathology		
- Stage IV (versus stage ≤ 3)	5.448 (1.932-15.357)	**0.001**
Postoperative characteristics		
Length of stay at the hospital (days)	1.041 (1.004-1.0794)	**0.031**
Length of stay at ICU (≥ 5 days (n))	1.016 (0.123-8.417)	0.988
Readmission to the hospital (n)	2.071 (0.702-6.107)	0.187
Complications (n)	2.752 (1.075-7.040)	**0.035**
- Clavien Dindo Score 1-2 (n)	2.269 (0.927-5.553)	0.073
- Clavien Dindo Score 3-4 (n)	1.445 (0.499-4.183)	0.498
Reoperation / reintervention (n)	1.497 (0.516-4.342)	0.457

Values are expressed as numbers (percentage) or median with inter quartile range. BMI, Body Mass Index; ASA, American Society of Anesthesiologists; ICU, Intensive Care Unit. OR, odds ratio; CI, 95% confidence interval.

Readmissions

Thirty patients (13.5%) were readmitted to the hospital within 30 days following surgery. After readmission 83.3% of the patients survived the first year. Readmission was not associated with worse one-year survival (p=0.187; table 2).

Independent risk factors for mortality at one year

All survivors of primary surgery were added to the logistic regression analyses with the outcome: mortality at one year. In univariate analysis ASA classification, Charlson Comorbidity Index, stage IV disease, length of stay at the hospital, and postoperative complications were associated with mortality at one year (table 2). ICU stay of more than 5 days, reoperations and readmissions were not associated with one year mortality. Variables added to the multivariate analysis were: ASA classification, stage IV disease and postoperative complications; Charlson Comorbidity Index and length of stay at the hospital were excluded from the analysis because of a high correlation with the other variables. For patients who survived the primary surgery, all three included parameters were independently associated with mortality at one year with an odds ratio of 5.716 ((95% CI 1.82-17.642), p=0.002) for stage IV disease; OR 4.112 ((1.308-12.930), p=0.016) for postoperative complications and 2.453 ((1.002-6.008), p=0.050) for ASA classification (table 3).

Table 3. Multivariable logistic regression of factors associated with one year mortality

Variable	OR (95% CI)	P-value
ASA classification (score)	2.453 (1.002-6.008)	0.050
Stage IV disease (yes)	5.716 (1.82-17.642)	0.002
Complication (yes)	4.112 (1.308-12.930)	0.016

OR, odds ratio; CI, 95% confidence interval.

DISCUSSION

This is the first study to demonstrate that after discharge from the hospital after colorectal cancer surgery in elderly patients, 10% of the patients die within one year after discharge. Tumor stage, postoperative complications, and ASA classification were associated with worse one-year outcome in survivors of the early postoperative period. Patients who died during the early postoperative period all had high degree complications, whereas once they had survived this period one year survival was equal after high or low degree complications.

Length of ICU stay was not associated with a worse outcome at one year. This indicates that if a patients survives prolonged ICU-stay, the prognosis for the next year is comparable to others. However, no information about quality of life after (prolonged) ICU stay is known. A study by Montuclard et al. concluded that prolonged ICU stay (> 30 days) in elderly patients (≥70 years old) was associated with an acceptable quality of life (QoL)[14], but emerging evidence suggests that (prolonged) ICU stay is associated with a decreased quality of life known as the Post-Intensive Care Syndrome (PICS).[15-17]

Dekker et al. demonstrated a slightly higher one-year mortality rate of 23.2% and 20.1% in elderly (≥ 75 years) colon respectively rectal cancer patients.[5] Factors that were significantly associated with an impaired one-year outcome in their study were male gender (in rectal cancer surgery), increased age, and tumor grade (in both colon and rectal cancer surgery). When patients survived the first year after surgery, survival was comparable for both the older and younger patients in both colon and rectal cancer surgery.[5] In a study among patients of 70 years or older who underwent non-cardiac surgery, postoperative pulmonary and renal complications also proved to be independently associated with a decreased long-term survival and a hazard ratio of 2.41 and 6.07 ($p<0.001$), respectively.[18]

It has been demonstrated that elderly patients are more likely to be readmitted to the hospital compared with younger patients.[19] Furthermore, readmission was found to be strongly associated with a higher one-year mortality rate with an adjusted OR of 2.44 (95% CI 2.25-2.65).[20] The reasons for readmission were comparable with those in our study, but readmission was not associated with a worse one-year outcome in our study which only included elderly (unadjusted OR 2.07 (0.70-6.11), $p=0.187$).

The surgical treatment of colorectal malignancies in the aging population remains a formidable challenge, where the chances of a successful outcome with a good quality of the remaining life span need to be weighed against the risk of potential complications with a detrimental outcome. Present day informed consent procedures and shared decision making with patients and relatives require an optimal knowledge of factors influencing the outcome of surgical procedures. The management of the older patient requires a stepwise approach at different stages. In the preoperative stage an optimal risk assessment is necessary either to decide to exclude the patient from surgery based on morbidity profiles, or to define the level of needed care tailored on patients' clinical and physical status. An individualized prehabilitation program should guarantee an optimization of the preoperative nutritional and cardiopulmonary status. In the perioperative stage, state-of-the-art surgical and anaesthesiological techniques are obligatory and every effort should be put in the prevention, early detection and containment of perioperative complications.

Early identification of patients at risk for an adverse perioperative course is paramount importance. In patients with considerable comorbidity a multidisciplinary approach may be opted for to optimize the preoperative condition and to prevent (comorbidity-related) postoperative complications. A patient-tailored approach with special attention for perioperative care is essential in the elderly.

In this study we demonstrated that once the patient survives the colorectal surgery, albeit after reoperation or prolonged ICU care, survival during the first year after discharge is comparable to that of others. Complications after surgery predict an increased risk of death, but mainly due to cardiopulmonary reasons. The life of an elderly patient suffering from postoperative complications after colorectal surgery is worth fighting for.

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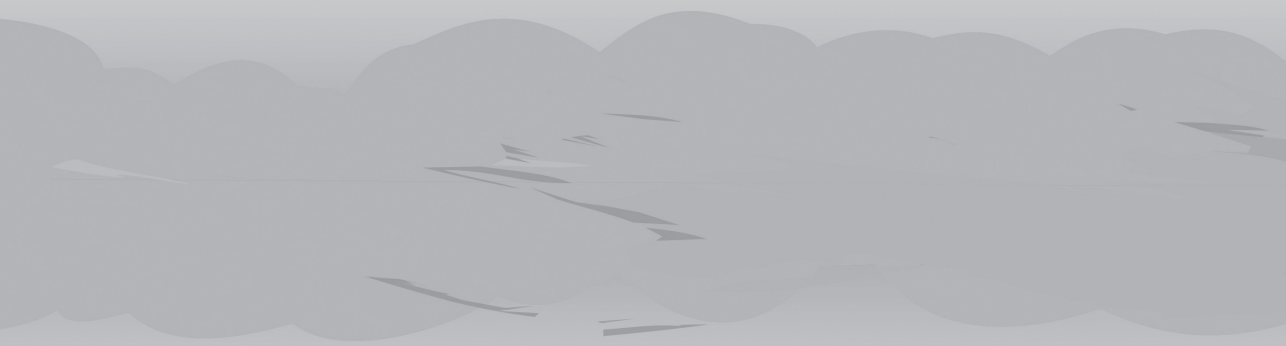
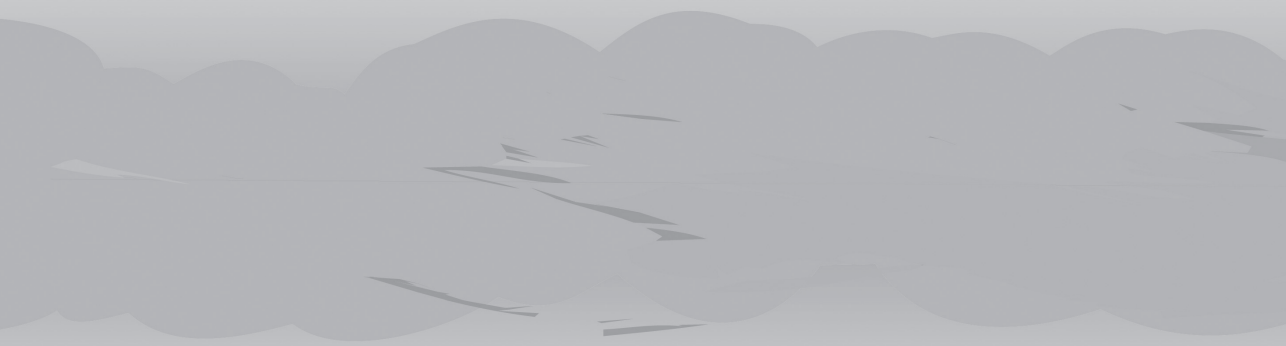


PART II

Visceral circulation and colorectal surgery



Chapter 4

Compromised visceral circulation does not affect the outcome after colorectal surgery

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ABSTRACT

Background

Anastomotic leakage is a serious complication after colorectal surgery and many risk factors have been identified. The aim of this study was to assess the association between visceral arterial occlusive disease and anastomotic leakage.

Methods

Pre-operative abdominal computed tomography scans from all consecutive patients who underwent colorectal surgery with anastomosis in 2010 were retrospectively analyzed.

Results

A total of 242 patients were included with a median age of 65 years (inter quartile range 55-74). Anastomotic leakage occurred in 14% (n=34). Mortality rate was 3% (n=8). There was no association between atherosclerosis of the visceral or iliac arteries and anastomotic leakage. Not even between right-sided or left-sided resections and total occlusion of the superior or inferior mesenteric artery, respectively.

Conclusion

Asymptomatic visceral artery occlusive disease is not a risk factor for anastomotic leakage after colorectal surgery and additional radiological imaging or percutaneous transluminal angioplasty for occluded visceral vessels are not indicated prior to colorectal surgery.

INTRODUCTION

Anastomotic leakage is the most feared and a potentially life-threatening complication after colorectal surgery. The incidence varies in the literature between 2% and 28%.[1-10] Many risk factors for the occurrence of anastomotic leakage after colorectal resections have been identified, including higher American Society of Anesthesiologists (ASA) score, coronary heart disease, malnutrition and excessive weight loss, higher body mass index (BMI) and emergency surgery.[1,3,4,6-8,10-13] Tissue perfusion is of importance in anastomotic healing. A compromised local vascular supply after bowel resection in combination with blood loss and hypotension may contribute to ischemia and secondary impaired healing of the newly created anastomosis.[14-18]. Atherosclerosis can cause tissue ischemia and is often suggested to be a risk factor for anastomotic leakage.[14,15,19,20] Recently Komen et al demonstrated that patients with higher calcium scores, secondary to a higher grade of atherosclerosis, have an increased risk of anastomotic leakage after colorectal surgery.[21] These authors suggested that when on preoperative imaging vascular lesions of the stem arteries become apparent, one may decide to create a primary stoma instead of an anastomosis in fear of dehiscence. It has however never been investigated whether the presence of actual vascular lesions indeed are associated with anastomotic healing failure, and should prompt us to decide for a primary stoma or preoperative dilation of stenosis. In a cohort of adult patients with colorectal disease who underwent colorectal surgery with primary anastomosis we aimed to investigate this possible association.

MATERIAL AND METHODS

All consecutive patients who underwent elective or emergency colorectal surgery with primary anastomosis for benign or malignant colorectal disease between January and December 2010 were retrospectively analyzed (n=302). These were all patients who were deemed suitable for anastomosis at the time of creating the anastomosis (i.e. in case of overall fragility, old age, major comorbidity or complicated surgery, a primary stoma was performed; these patients were excluded from this analysis. Also, in all patients the known adagium of a well circulated tensionless anastomosis was followed). Patients in whom a preoperative computed tomography (CT) scan was not performed or was of poor quality, were excluded from this study (n=60). In all these patients the preoperative CT scan was made for other purposes, and no specific attention was paid to the presence of vascular lesions. The possible association between such lesions and anastomotic failure was thus sought in a retrospective manner.

All demographic and clinical data, including operative reports, abdominal computed tomography reports and histological data were collected. Baseline and operation-related parameters included sex, age at surgery, smoking, alcohol, BMI, comorbidity, history of abdominal or vascular surgery, medication, surgical diagnosis, American Society of Anaesthesiologists risk class (ASA classification), surgical procedure, approach, type of anastomosis (i.e. end-to-end or side-to-side, stapled or hand-sewn), timing of surgery and creation of a protective ileostomy.

Preoperative CT imaging was performed on a sixteen and a two hundred fifty-six slice-MDCT scanner (Philips, Best, the Netherlands) with a slice thickness of algorithm of 3-5 mm with axial and coronal reconstructions. Scan delay-time was 60-70 seconds after intravenous injection of 100 ml of iobitridol (Xenetix 300, Guerbet Nederland BV), injected at a rate of 4.0 ml/s, using a mechanical power injector. Intravenous contrast was given in all patients, excluding those with proven allergy or renal failure. Gastro-intestinal contrast medium (1 l of oral contrast fluid (20 ml iobitridol 300 mg I/ml, Guerbet, diluted in 1 l of tap water)) was administered at least 1 hour prior to the CT-scan.

Preoperative CT-scans were in retrospect reviewed separately by two radiologists, who were blinded to the clinical information to prevent bias. Disagreement was resolved by discussion and consensus between the two radiologists.

The grade of stenosis in the celiac trunk, superior and inferior mesenteric arteries and common and internal iliac arteries was determined by the following formula: percent stenosis = (1 – (minimal diameter)/ (post-stenotic diameter)) × 100%, according to the NASCET criteria.[22-23] We also identified the nature of the plaque (calcified versus non-calcified).

Primary outcome measure was anastomotic leakage, which was defined as anastomotic dehiscence visualized at relaparotomy or endoscopy, or percutaneous or transanal drainage of pus or enteral contents.

Statistical analysis

The Mann-Whitney-U test was used for continuous data. The Chi-square test was used for binomial data. Values are given as number of patients or median and inter quartile range. All probability values are two-tailed. $P < 0.05$ was used as level of significance. The data was analyzed with SPSS statistical software (SPSS Statistics Version 17.0, Inc., Chicago, Illinois, USA).

Table 1. Baseline and operation-related characteristics

	All patients (n = 242)	No leakage (n = 208)	Anastomotic leakage (n = 34)	p-value
Age at surgery (years)	65 (55-74)	65 (55-74)	64 (57-76)	0.687
- Age ≥70 years (n)	90	76 (36.5%)	14 (41.2%)	0.743
- Age ≥80 years (n)	32	25 (12.0%)	7 (20.6%)	0.274
Sex				
- Male (n)	131	111 (53.4%)	20 (58.8%)	0.684
- Female (n)	111	97 (46.6%)	14 (41.2%)	
BMI (kg/m^2)	25.5 (23.0-28.4)	25.5 (22.9-28.4)	25.1 (23.1-28.7)	0.541
Smoking (n)[a]	44	36 (17.9%)	8 (23.5%)	0.590
Alcohol (n)[a]	98	83 (41.5%)	15 (44.1%)	0.922
Comorbidity				
- Diabetes mellitus (n)	143	123 (59.1%)	20 (58.8%)	1.000
- Hypertension (n)	164	142 (68.3%)	22 (64.7%)	0.830
- Peripheral arterial occlusive disease (n)	145	124 (59.6%)	21 (61.8%)	0.961
- Cardiac comorbidity (n)	159	139 (66.8%)	20 (58.8%)	0.474
ASA-score				
- ASA 1 (n)	44	39 (18.8%)	5 (14.7%)	0.744
- ASA 2 (n)	167	143 (68.8%)	24 (70.6%)	0.988
- ASA 3 (n)	31	26 (12.5%)	5 (14.7%)	0.936
Medication				
- Use of antihypertensive medication (n)	116	100 (48.1%)	16 (47.1%)	1.000
- Use of statins (n)	43	35 (16.8%)	8 (23.5%)	0.480
- Use of anticoagulant medication (n)	71	60 (28.8%)	11 (32.4%)	0.831
History of surgery				
- Abdominal surgery (n)	128	108 (51.9%)	20 (58.8%)	0.574
- Cardiovascular/ peripheral artery surgery (n)	20	16 (7.7%)	4 (11.8%)	0.643
Pathology				
- Benign (n)	113	103 (49.5%)	10 (29.4%)	0.046
- Malign (n)	129	105 (50.5%)	24 (70.6%)	0.046
Preoperative complication				
- No complication (n)	202	172 (82.7%)	30 (88.2%)	0.577
- Stenosis without symptoms (n)	11	11 (5.3%)	0 (0.0%)	0.353
- Mechanical ileus (n)	9	6 (2.9%)	3 (8.8%)	0.227
- Perforation (n)	14	14 (6.7%)	0 (0.0%)	0.245
- Ischemia (n)	3	2 (1.0%)	1 (2.9%)	0.896
- Fistula (n)	3	3 (1.4%)	0 (0.0%)	1.000
Approach				
- Laparotomy (n)	138	117 (56.3%)	21 (61.8%)	0.678

Table 1. Baseline and operation-related characteristics (continued)

	All patients (n = 242)	No leakage (n = 208)	Anastomotic leakage (n = 34)	p-value
- Laparoscopic (n)	89	78 (37.5%)	11 (32.4%)	0.700
- Converted (n)	14	12 (5.8%)	2 (5.9%)	1.000
Timing				
- Elective (n)	205	174 (83.7%)	31 (91.2%)	0.383
- Urgent (n)	36	33 (15.9%)	3 (8.8%)	0.418
Ileostomy (n)	19	11 (5.3%)	8 (23.5%)	0.001

Values are given as number of patients (n) and percent (%) of group. Age and BMI are expressed in median (inter quartile range) and were tested with the Mann-Whitney-U test. Binomial data was tested with the Chi-square test. *BMI* body mass index, *ASA* American Society of Anaesthesiologists.
[a] Data does not add up to *234* because of occasional missing data.

RESULTS

Between January and December 2010 a total of 302 patients underwent partial colectomy with primary anastomosis for benign or malignant colorectal disease or restoration of large bowel continuity. Two hundred and forty two patients (80%) had undergone a preoperative CT scan for other reasons (mostly for staging of colorectal cancer) but of adequate quality to retrospectively identify vascular lesions. Baseline and operation-related characteristics are summarized in table 1. There were no differences in baseline characteristics between patients with and without pre-operative CT scans.

Bowel resections were right-sided in 104 patients (43%); left-sided in 96 patients (40%) of which 16 patients underwent low anterior resection; subtotal colectomy was performed in 7 patients (3%); 35 patients underwent restoration of large bowel continuity (14%). Anastomotic leakage was seen in 34 of 242 patients (14%); mortality after anastomotic leakage was 12% (n=4). The overall mortality rate was 3% (n=8).

Visceral circulation of all patients

Of 242 patients, 98 patients (41%) had more than 50% arteriosclerotic lesions in one or more of the visceral arteries (table 2). Of this group 15 suffered leakage (15%) versus 19 of 144 patients (13%) with less than 50% vascular lesions (not significant). Complete arterial occlusion was mostly seen in the inferior mesenteric artery (6%; n=14). There was also no association between the occurrence of anastomotic leakage and the nature of the plaques: calcified or non-calcified (results not shown). A subanalysis for only patient with benign disease versus malignant disease also did not show any association between vascular damage and the occurrence of anastomotic leakage (data not shown).

Table 2. Grade of stenosis – all patients

	All patients (n = 242)	No leakage (n = 208)	Anastomotic leakage (n = 34)	p-value
Celiac trunc[a]				
- Soft tissue band	30	24 (11.7%)	6 (17.6%)	0.484
- No stenosis	121	104 (50.5%)	17 (50.0%)	1.000
- < 50 %	67	58 (28.2%)	9 (26.5%)	1.000
- ≥ 50 %	47	40 (19.4%)	7 (20.6%)	1.000
- 100 % (total occlusion)	4	3 (1.5%)	1 (2.9%)	1.000
Superior mesenteric artery[a]				
- No stenosis	180	153 (74.3%)	27 (79.4%)	0.669
- < 50 %	52	46 (22.3%)	6 (17.6%)	0.697
- ≥ 50 %	8	7 (3.4%)	1 (2.9%)	1.000
- 100 % (total occlusion)	0	0 (0%)	0 (0%)	-
Inferior mesenteric artery[a]				
- No stenosis	101	87 (42.2%)	14 (41.2%)	1.000
- < 50 %	79	66 (32.0%)	13 (38.2%)	0.606
- ≥ 50 %	46	40 (19.4%)	6 (17.6%)	0.994
- 100 % (total occlusion)	14	13 (6.3%)	1 (2.9%)	0.703
Common iliac artery[b]				
- No stenosis	125	106 (52.2%)	19 (55.9%)	0.833
- < 50 %	93	81 (39.9%)	12 (35.3%)	0.749
- ≥ 50 %	18	15 (7.4%)	3 (8.8%)	1.000
- 100 % (total occlusion)	1	1 (0.5%)	0 (0%)	1.000
Left internal iliac artery[c]				
- No stenosis	122	105 (51.5%)	17 (51.5%)	1.000
- < 50 %	82	69 (33.7%)	13 (39.4%)	0.656
- ≥ 50 %	31	29 (14.1%)	2 (6.1%)	0.316
- 100 % (total occlusion)	3	2 (1.0%)	1 (3.0%)	0.888
Right internal iliac artery[d]				
- No stenosis	125	107 (52.2%)	18 (52.9%)	1.000
- < 50 %	86	73 (35.6%)	13 (38.2%)	0.918
- ≥ 50 %	24	22 (10.7%)	2 (5.9%)	0.573
- 100 % (total occlusion)	4	3 (1.5%)	1 (2.9%)	1.000
No clinical relevant vascular damage (<50% stenosis)	144 (59.5%)	125 (60.1%)	19 (55.9%)	0.783
Stenosis ≥50% in ≥1 artery	98 (40.5%)	83 (39.9%)	15 (44.1%)	0.783
Stenosis ≥50% in ≥2 arteries	47 (19.4%)	41 (19.7%)	6 (17.6%)	0.961
Stenosis ≥50% in ≥3 arteries	24 (9.9%)	22 (10.6%)	2 (5.9%)	0.589
Stenosis ≥50% in ≥4 arteries	13 (5.4%)	13 (6.3%)	0 (0.0%)	0.641
Total occlusion of ≥1 artery	21 (8.7%)	17 (8.2%)	4 (11.8%)	0.718

Table 2. Grade of stenosis – all patients (continued)

	All patients (n = 242)	No leakage (n = 208)	Anastomotic leakage (n = 34)	p-value
Total occlusion of ≥2 arteries	2 (0.8%)	2 (1.0%)	0 (0.0%)	1.000

Values are given as number of patients (n) and percent (%) of group. Data tested with the Chi-square test.
[a] Data does not add up to *240* because of occasional missing data; [b] Data does not add up to *237* because of occasional missing data; [c] Data does not add up to *238* because of occasional missing data; [d] Data does not add up to *239* because of occasional missing data.

Right or left sided colectomy

A subanalysis was performed for patients who underwent right sided hemicolectomy (group A; n=104) or left sided colectomy (group B; n=96). The results of preoperative CT scans are depicted in table 3 (group A: right sided colectomy) and table 4 (group B: left sided colectomy).

Table 3. Grade of stenosis - Group A: Right sided colectomy (ileocecal resection, right hemicolectomy, transverse colon resection)

	All patients (n = 104)	No leakage (n = 88)	Anastomotic leakage (n = 16)	p-value
Superior mesenteric artery[a]				
- No stenosis	65	54 (62.1%)	11 (68.8%)	0.820
- < 50 %	30	26 (29.9%)	4 (25.0%)	0.924
- ≥ 50 %	8	7 (8.0%)	1 (6.3%)	1.000
- 100 % (total occlusion)	0	0 (0%)	0 (0%)	-

Values are given as number of patients (n) and percent (%) of group. Data was tested with the Chi-square test. [a] Data does not add up to *103* because of occasional missing data.

Table 4. Grade of stenosis - Group B: Left sided colectomy (transverse colon resection, left hemicolectomy, sigmoid, (lower) anterior and resection)

	All patients (n = 96)	No leakage (n = 82)	Anastomotic leakage (n = 14)	p-value
Inferior mesenteric artery				
- No stenosis	47	39 (47.6%)	8 (57.1%)	0.676
- < 50 %	26	22 (27.2%)	4 (28.6%)	1.000
- ≥ 50 %	19	17 (21.0%)	2 (14.3%)	0.828
- 100 % (total occlusion)	4	4 (4.9%)	0 (0%)	0.897

Values are given as number of patients (n) and percent (%) of group. Data was tested with the Chi-square test.

Group A: right-sided colectomy (ileocecal resection, right hemicolectomy and transverse colon resection).
The prevalence of anastomotic leakage was 15% (16 of 104 patients). At baseline there were no differences in possible risk factors other than arterial occlusive disease between patients with and patients without anastomotic dehiscence (data not shown). Of 104 patients with right sided colectomy, 8 patients (8%) had 50% stenosis or more of the superior mesenteric artery. Anastomotic leakage was seen in 1 of these patients (13%), versus 15 of 95 patients without relevant vascular damage and anastomotic leakage (16%). Mortality rate in patients with anastomotic leakage after right-sided colectomy was as high as 25% (n=4).

Group B: left-sided colectomy (transverse colon resection, left hemicolectomy, sigmoid, anterior and lower anterior resection).
The prevalence of anastomotic leakage was 15% (14 of 96 patients). Again there were no differences in other risk factors at baseline. Of 96 patients who received a left-sided anastomosis, 23 patients (24%) had 50% stenosis or more of the inferior mesenteric artery. Anastomotic leakage was seen in 2 of these 23 patients (9%) versus 12 of 73 patients with anastomotic leakage without relevant vascular damage (16%). No patients in this group died.

In both groups, no significant differences were seen between the presence of vascular damage in any of the other main abdominal vessels and the occurrence of anastomotic leakage (data not shown).

DISCUSSION

Atherosclerosis of the mesenteric arteries is a frequently observed condition in asymptomatic patients. Stenosis in one or more mesenteric arteries is usually well tolerated because of a sufficient collateral network.[27-30] But still atherosclerosis is often suggested to be associated with anastomotic dehiscence, although little is known in the literature on this subject. During colorectal surgery the normal blood supply to the intestines is disrupted and diminished blood flow may cause local intestinal ischemia. Possibly in cases where blood flow is already critical, i.e. due to a pre-existing compromised visceral circulation, the intestinal anastomosis is at risk for inadequate healing and subsequent anastomotic leakage. However, in this study among 242 patients undergoing colorectal anastomosis we could not find any association between an increased grade of atherosclerosis in one of the main abdominal arteries and the risk for anastomotic leakage.

In the literature little is found about the consequences of impaired vascularisation in patients undergoing abdominal surgery. In acute aortic repair surgery occlusive ischemic colitis may occur due to acute occlusion or ligation of the inferior mesenteric artery. Although not funded by data it is general knowledge that in patients with an already occluded inferior mesenteric artery at the time of aortic repair, sigmoidal ischemia is rare due to an already newly formed collateral system. It seems from our findings that the same mechanism accounts for the absence of increased anastomotic leakage rate after colorectal surgery in patients with pre-existing visceral vascular damage.

Komen et al. used calcium scores to analyze the atherosclerotic load in abdominal vessels.[21] They identified calcium score, calcium mass and calcium volume as independent risk factors for anastomotic leakage in a group of 122 patients. The authors suggest that additional imaging of the iliac vessels in patients undergoing rectal surgery is justified, in order to quantify atherosclerotic calcifications in iliac arteries. However, in our study, using other method to measure degree of atherosclerosis, we could not find any relation between radiologically visible atherosclerosis and anastomotic dehiscence. Therefore it does not seem necessary to routinely extend preoperative staging imaging of the liver down to the iliac vessels.

In this study, overall leakage rate of 14% was relatively high, but no risk factors (table 1) for anastomotic leakage were identified. There is no clear explanation for this rate. There was also no difference in leakage rate between right and left sided colectomy. The authors suggest that this may also be due to patient selection. In high risk patients who underwent left sided colectomy, primary stoma was more often performed. Furthermore, transverse colon resections were scored in both right and left sided colectomy. Left sided colectomy in our study was defined as transverse colon resection, left hemicolectomy, sigmoid, anterior and lower anterior resection.

Limitation of this study is its retrospective character. Although patients with poor-quality CT scans were excluded from further analysis there was variation in CT scans and differences in slice thickness. Therefore we excluded patients with a too low quality preoperative CT scan form this analysis. In the selected 242 CT scans, calcified and non-calcified plaques and the degree of stenosis were clearly evaluated. In patients in whom perioperative (vascular) findings were critical or surgery was complicated, a primary stoma was performed rather than the creation of an anastomosis. Proper patient selection may therefore contribute to the absence of an association between vascular damage and anastomotic dehiscence. However, in our patient group still 41% had extensive visceral arterial occlusive disease. Also, with a relatively high leakage rate in our study the results

did not even show a trend towards statistical significance. Therefore, the found absence of an association seems reliable. It is likely that other clinical parameters may indicate vascular disease just as well, and that intra-operative findings may be of more importance to determine a well vascularised anastomosis.

CONCLUSION

In conclusion, compromised visceral circulation due to a higher grade of visceral artery occlusive disease is not associated with anastomotic leakage after colorectal surgery. Additional radiologic imaging (i.e. CT in arterial phase) to assess vascular status of the patient prior to colorectal surgery does not seem indicated. Vascular lesions of the visceral arteries need not be taken into account in risk assessment of individual patients. Also, if vascular damage is seen on preoperative staging imaging there is no indication for percutaneous transluminal angioplasty (PTA) of the visceral vessels prior to partial colectomy.

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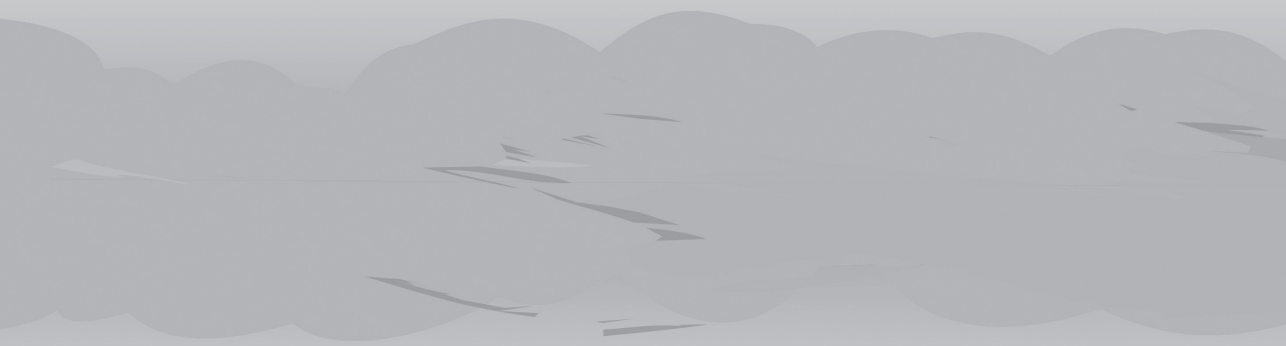

Chapter 5

Sidestream dark field imaging of the serosal microcirculation during gastrointestinal surgery

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ABSTRACT

Aim

To describe the serosal microcirculation of the human bowel using sidestream dark field imaging, a microscopic technique using polarized light to visualize erythrocytes through capillaries, and to compare its feasibility to the current practice of sublingual microcirculatory assessment.

Methods

In seventeen patients sidestream dark field measurements were performed during gastrointestinal surgery. Microcirculatory parameters like microvascular flow index (MFI), proportion of perfused vessels (PPV), perfused vessel density (PVD) and total vessel density (TVD) were determined for every patient, sublingually and on the bowel serosa.

Results

In total 60 measurements were done on the bowel of which 8 (13%) were excluded, 5 due too much bowel peristalsis, 3 because of pressure artifacts. Image stability (Pixel loss per image; Bowel: 145 (CI 126-164) versus Sublingual: 55 (CI 41-68); P<0.001) and time to acquire a stable image (Bowel: 108 (CI 53-163) seconds versus Sublingual: 46 (CI 29-64) seconds; P=0.03) were in favor of sublingual measurements. No difference in the MFI was observed (Bowel: 2.9 (IQR 2.87-2.95) versus Sublingual: 3.0 (IQR 2.91-3.0); P=0.081). There was a difference in the PPV (Bowel: 95% (CI 94-96%) versus Sublingual: 97% (CI 97-99); P<0.001), PVD (Bowel: 12.9mm/mm2 (CI 11.1-14,8) versus Sublingual 17.4mm/mm2 (CI 15.6-19.1); P=0.003), and the TVD (Bowel:13.6mm/mm2 (CI 11.6-15.6) versus Sublingual: 17.7mm/mm2 (CI 16,0-19,4); P=0.008).

Conclusion

Sidestream dark field imaging is a very promising technique for bowel microcirculatory visualization and assessment. It is comparable to sublingual assessment and the analysis produces similar outcome with slightly differed anatomical features.

INTRODUCTION

Anastomotic leakage after gastrointestinal surgery is a serious complication with an incidence of around 10% after colorectal resection and is associated with increased morbidity[1] and hospital mortality.[2-3] Moreover, anastomotic leakage after colorectal surgery is associated with a worse long-term survival and a higher rate of recurrence.[4] Amongst many factors, microvascular alterations may play an important role in bowel anastomotic healing and adequate tissue oxygenation is imperative for healing of bowel anastomoses after gastrointestinal surgery.[5-8] For a long time, intra-operative hemodynamic assessment has been limited to systemic measurements, such as blood pressure, central venous pressure and heart rate. Recently, a more organ specific approach focusing on local oxygen delivery and microcirculatory perfusion has gained interest in perioperative and intensive care monitoring.[9-14] Peri-anastomotic microvascular alterations caused by manipulation of the bowel, or due to vascular dissection, may result in a local inability to regulate oxygen delivery despite adequate macrohemodynamic conditions and oxygen supply. This could result in tissue hypoxia and anastomotic deterioration. For years bowel tissue perfusion and vitality was macroscopically assessed by surgeons before deciding to anastomose the bowel or remove dubiously perfused segments. Several techniques and devices have been studied to objectify bowel perfusion and viability, which have not led to a unanimous successful device.[15] Sidestream Dark Field (SDF) imaging is a promising, non-invasive method to visualize the microcirculation and assess its function and anatomy. In contrast to other methods, one is able to visually assess the micro-vessel architecture, flow and its functionality.[16] SDF-imaging is currently mainly applied sublingually to assess microvascular dysfunction in septic patients on intensive care units.[9,16,17] Little is known about the gastrointestinal microcirculation in humans visualized with SDF-imaging and is mostly performed in a small number of animal studies.[18,19] In humans, SDF imaging has previously only been used on the mucosal side on stomas and transanally on the rectal mucosa.[14,20,21] The human gastrointestinal microcirculation has never been assessed with SDF-imaging intra-operatively, when the serosal side is also accessible for assessment. Therefore, the goal of this study is to describe the serosal microcirculation of the human bowel using SDF-imaging during gastrointestinal surgery and compare its assessment and feasibility to the current practice of sublingual microcirculatory assessment.

MATERIAL AND METHODS

Setting and patient selection

A prospective, single center, observational, clinical study was performed between June and December 2014 in patients undergoing elective gastrointestinal surgery. Surgical procedures included were: All forms of open colorectal surgery, pylorus presevering pancreaticoduodenectomy (PPPD) and laparoscopic procedures with extracorporeal creation of the bowel anastomosis. This study was performed in a tertiary teaching hospital (St. Antonius Hospital, Nieuwegein, the Netherlands) after approval of the united medical ethical committees and the local research and development committee. All patients gave written informed consent.

Imaging technique

Sidestream dark field imaging consists of a handheld device that illuminates an area of interest by surrounding a central light guide with concentrically placed light emitting diodes(LEDs), which thus provide SDF-illumination. If the wavelength within the hemoglobin absorption spectrum is chosen, erythrocytes will appear dark and leucocytes may be visible as refringent bodies. The vessel walls itself are not visualized directly, although faint contours can be identified depending on the presence of intravascular erythrocytes. The lens system in the light guide core is optically isolated from the illuminating outer ring thus preventing tissue surface reflections to enter the center of the light guide. The SDF is fitted with an analog video camera that needs to be digitalized by separate analog to digital convertor devices for off-line image analysis.[22,23] The SDF-imaging device used in this study, the MicroScan (MicroVision Medical, Amsterdam, the Netherlands) is CE-certificated.

Protocol and image acquisition

All surgical procedures were performed in accordance with standard local protocols. All patient data was recorded automatically and continuously by a patient data-management system. In case of high-risk procedures, an arterial catheter was inserted in the radial artery and connected to the FloTrac™/Vigileo™ system (Edwards Lifesciences, USA) to obtain the cardiac index (CI) and stroke volume variation (SVV). Anesthesia-related hypotension (≥20% decrease in mean arterial pressure (MAP) or MAP <60 mmHg), a decrease in CI or increase in SVV was treated until the patient showed stable hemodynamic parameters, before measurements with the SDF-imaging device were started. During measurements, special care was taken to avoid pressure artifacts, adhering to the standard operating procedure previously described by Trzeciak et al[24] and recommended in the roundtable conference.[16] A laparoscopy camera cover over the SDF imaging device was used to create

a sterile work field for the serosal measurements. This is a disposable sterile endoscopic camera protection cover, which can be used during laparoscopic surgery. This cover can also be used to protect the SDF imaging device during measurements. Furthermore, the sterile disposable lens cover was pre-heated to body temperature, secretions or blood on the bowel surface were removed with gauze and sterilized saline was applied at the surface of interest. After obtaining good image focus, the probe was pulled back gently until contact was lost and then slowly advanced again to the point at which contact was regained. This was done because small alteration in flow of the larger venules may indicate pressure artifacts. Image acquisition with the SDF-imaging device included three good quality and stable visual recordings per area of interest. These were stored under a random number and the locations of all measurements were noted. Two investigators separately analyzed these images(off-line) using the AVA 3.2 Software program (Microvision Medical, Amsterdam, The Netherlands).[25] Sublingual and bowel serosal measurements were directly successively performed. Time until stable image and completion of measurements were noted for each measurement as indicative of the difficulty of obtaining images. Image stability was assessed by measuring image drift. Image drifting during automated image stabilization (AVA 3.2 software) was measured as the translation (in pixels) in either x- or y direction of an image with respect to the first image of a video sequence, resulting in loss of pixels per image.[25]

Quantifying Microcirculation

In a roundtable conference, international experts reached consensus on how to evaluate the microcirculation using SDF-imaging.[16] All recommendations given were implemented. Video clips were directly saved as digital AVI-DV files to a hard drive of a personal computer using an analog-to-digital converter (Canopus, Kobe, Japan) and the freeware program WinDV (http://windv.mourek.cz). A 5 times optical magnification was used, producing images representing approximately 0.94 x 0.75 mm of tissue surface. Microvascular flow index (MFI), proportion of perfused vessels (PPV), perfused vessel density (PVD) and Total vessel density (TVD) were determined for every patient sublingually and on the bowel serosa. The semi quantitative microvascular flow index (MFI), ranging from 0 (no flow) to 3 (continuous flow) is based on the determination of the predominant type of flow in four quadrants. The MFI is the sum of these scores divided by the number of scored quadrants (figure 1).

PPV was obtained by scoring all vessels with a flow score greater than 1 (figure 2), scored semi quantitative, ranging from 0 (no flow) to 3 (continuous flow) together with the MFI, this provided information on convection. Thereby quantifying the flow or movement of erythrocytes within the microvessels. Total vessel density (TVD) and perfused vessel den-

sity (PVD), both expressed in mm/mm2, provided information on diffusion (figure 2) by showing density and vessel distance. Perfused vessel density (PVD) can be calculated by multiplying vessel density by the proportion of perfused vessels(PPV). The image analysis has previously been described in detail elsewhere.[25] Each score was determined for small micro vessels with a cut-off diameter of 25 µm. For each area of interest three video files were recorded and the scored indices, MFI, PPV, TVD, PVD were averaged resulting into one MFI, PPV, TVD and PVD per area of interest per time point. This was done because of the intrinsic variability of the microcirculation and that several sites of the organ of interest should be averaged as a recommendation of the roundtable conference.[16]

Statistical analysis

Data are presented in medians and interquartile ranges (IQR) for MFI and as the mean for other parameters, unless indicated otherwise. Nonparametric tests were used for MFI and the paired t-test was used for the other data. The statistical package for social sciences (IBM SPSS 20 statistics) was used for statistical analysis. A two-sided p-value <0.05 was considered statistically significant.

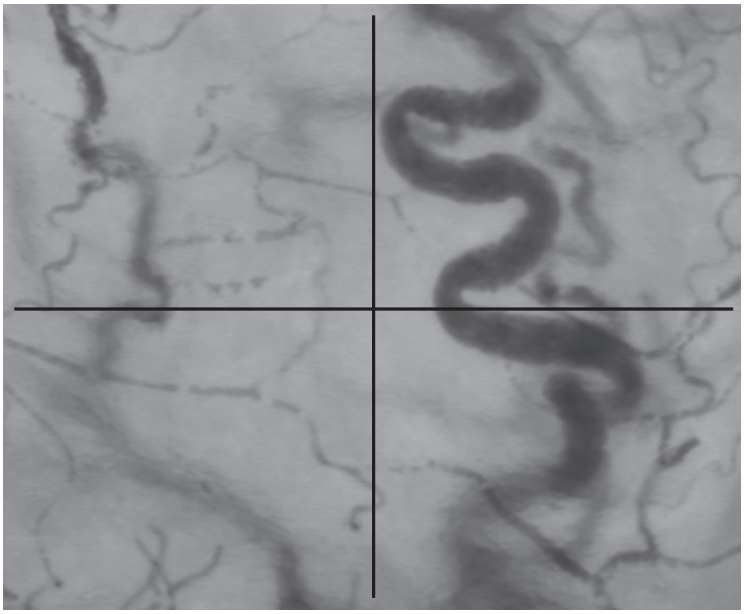

Figure 1. Serosal microcirculation. Determination of mean flow index (MFI) score. The image is divided into four quadrants and the predominant type of flow (absent = 0, intermittent = 1, sluggish = 2, and normal = 3) is assessed in each quadrant. The MFI score represents the averaged values of the four. A 25 µm cut-off is used to separate small vessels (mostly capillaries) from large vessels (mostly venules).

Figure 2. Serosal microcirculation. Microvascular density is calculated as the microvascular length (mm) divided by the imaged tissue area (mm2). PPV = PVD / TVD x 100 (%). PPV, proportion perfused vessels; PVD, perfused vessel density (mm/mm2); TVD, total vessel density (mm vessel/mm2). Perfusion of each vessel is scored semi quantitatively as follows: 0 no flow (no flow present for the entire duration of the clip), 1 intermittent flow (flow present 50% of the duration of the clip), 2 sluggish flow (flow present 50% but 100% of the duration of the clip or very slow flow for the entire duration of the clip), and 3 continuous flow (flow present for the entire duration of the clip). Flow in the PPV and PVD was obtained by scoring all vessels with a flow score greater than 1.

RESULTS

Twenty patients were screened and considered eligible. Because three patients withheld informed consent, seventeen were enrolled. Baseline characteristics are summarized in table 1. Six patients underwent laparoscopic colorectal surgery and measurements were done after the sigmoid was brought out through a Pfannenstiel incision for tumor resection and preparation of the anastomosis. Two patients underwent diagnostic laparotomy to be assessed if they were eligible for hyperthermic intraperitoneal chemotherapy (HIPEC). The remaining nine patients underwent laparotomy, both the sublingual and bowel measurements were performed towards the end of the operation. An accessible piece of bowel, either colon or small intestine, with sufficient distance to the tumor or anastomosis was used.

Table 1. Baseline characteristics

Gender male/female (n)	10/7
Age (years)	69 (80-60)
Procedures	
Laparoscopic low anterior resection (%)	3 (17.6)
Laparoscopic sigmoid resection (%)	3 (17.6)
PPPD* (%)	3 (17.6)
Hemicolectomy (%)	6 (35.3)
Diagnostic laparotomy (%)	2 (11.8)
BMI (kg/m^2)	26 (19-39)
Epidural analgesia	14 (82.4)
Smoker	3 (17.6)
Hypertension	9 (52.9)
Diabetes	4 (23.5)
COPD	4 (23.5)

All data are presented as mean (range) or as absolute numbers.
* Pylorus preserving pancreaticoduodenectomy

All measurements were performed under normal hemodynamic conditions (table 2). Eleven patients had an indication for cardiac output monitoring. There was an equal distribution in measurements on the colon (30) and small intestines (30). In total, 60 measurements were performed on the bowel, of which eight (13%) were excluded (five due to extensive bowel peristalsis, three because of pressure artifacts). In one patient no sublingual measurements were performed, because of technical problems.

Table 2. Systemic haemodynamic characteristics during microcirculatory measurements

Heart rate (beats/min)	64 ± 12
Systolic arterial pressure (mmHg)	110 ± 6
Diastolic arterial pressure (mmHg)	56 ± 10
Mean arterial pressure (mmHg)	74 ± 8
Central venous pressure (mmHg)	10 ± 4.6
Core temperature (°C)	36.1 ± 0.68
Cardiac index (L/min.m^2)	2.3 ± 0.4
Stroke volume variation (%)	11 ± 6
Haemoglobine (mmol/l)	7.3 ± 1.3
Haematocrit (%)	34 ± 6
Norepinepherine use (n)	8
Norepinepherine dose (µg/kg.min)	0.045 ± 0.037

There was a significant difference in image drifting between the bowel serosa and sublingual area expressed in pixel loss per image: 145 (95% confidence interval (CI) 126-164) versus 55 pixels (95% CI 41-68), p<0.001. The time to acquire a stable image was significantly longer on the bowel compared to the sublingual area 108 (95% CI 53-163) seconds versus 46 (95% CI 29-64) seconds, p=0.03. There was no significant difference in the MFI on the bowel compared with the MFI of the sublingual area 2.9 (interquartile range (IQR) 2.87-2.95) versus 3.0 (IQR 2.91-3.0), p=0.081. Significant differences were observed in the bowel PPV (95% (95% CI 94-96)) versus sublingual (97% (95% CI 97-99), p<0.001) and the bowel TVD (13.6 mm/mm2 (95% CI 11.6-15.6)) versus sublingual (17.7 mm/mm2 (95% CI 16.0-19.4)), p=0.008. PVD was significantly higher in the sublingual area (17.4 mm/mm2 (95% CI 15.6-19.1)) compared with the bowel (12.9 mm/mm2 (95% CI 11.1-14.8)), p=0.003 (table 3).

Table 3. Microcirculation and obtained image data

	Bowel	Sublingual	Difference (95%-CI)	p-value
MFI	2.9	3	0.1	0.081
PPV (%)	95	97	-0.3 (0.04 to -0.01)	<0.0001
TVD (mm/mm^2)	13.6	17.7	-4.0 (-6.9 to -1.2)	0.008
PVD (mm/mm^2)	12.9	17.4	-4.4 (-7.1 to -1.7)	0.003
Image drift (pixels)	145	55	90 (70 to 109)	<0.0001
Time to stable image (seconds)	108	46	62 (5.6 to 118.4)	0.033

Data presented; MFI: microvascular flow index (median), PPV: proportion of perfused vessels (mean), TVD: Total vessel density (mean), PVD: perfused vessels density (mean), CI: confidence interval

Differences were observed in the sublingual microvascular anatomy compared to the bowel serosa, apart from the apparent difference in microvascular density as expressed in the TVD and PVD. Vessels are often more longitudinally oriented in the intestines and curled in the sublingual area (Video Example 1). Connective tissue of the serosal side of the gut is often thicker than the sublingual mucosa, but this gives no hindrance in microvascular assessment even at the taenia libera of the colon. Connective tissue is sometimes seen as a light marking on the forefront image with the microcirculation of the bowel clearly on the background. This was not observed in the sublingual area. Edema and hemorrhage of the intestinal wall or sublingual mucosa made the microvascular assessment more challenging, but not impossible.

DISCUSSION

This is the first study that reports on SDF-imaging on the human intestinal serosa. These results demonstrate that serosal microvascular imaging with a SDF-device is feasible and similar to sublingual assessment. The microcirculatory anatomy could clearly been visualized and the indices for diffusion (PVD and TVD) and convection (PPV and MFI) known from sublingual assessment were used and here from reported.

In septic patients, microcirculatory alterations have been described using SDF-imaging (22), even though systemic hemodynamic parameters, like blood pressure, central venous pressure and heart rate, may be within an acceptable range.[26] Previous studies using SDF-imaging hypothesize that altered microcirculation, particularly heterogeneity of flow, plays an important role in the onset of sepsis and pathogenesis of organ failure.[20,27] With a similar, but more invasive visual technique, sepsis-induced microcirculatory dysfunction in an animal model was shown to be related with impaired anastomotic healing.[28] Local disruption of the microcirculation without sepsis or macrohemodynamic alterations have also been reported to lead to anastomotic leakage in colorectal surgery and upper GI-surgery using laser doppler flowmetry on the intestinal serosa.[10,29] Several non-invasive techniques have been assessed in clinical research to qualify and quantify bowel perfusion and viability, but are either difficult to implement in daily practice, have large inter-individual variation in measurements or have an insufficient accuracy of the technique to be useful in clinical practice.[15] Using intravenous indocyanine green, near-infrared angiography has been shown to be an accurate tool for assessing microperfusion of the bowel.[30] Recent studies showed that using this technique for visualising perfusion of the planned site of the anastomosis, led to change in surgical plan in between 8 and 19 percent of patients, resulting in lower anastomotic leak rates than those reported in the literature.[31-33] Realtime near infrared indocyanine fluorescence angiography has the advantage over SDF imaging that it is feasible in open and laparoscopic surgery without the necessity of direct contact with the bowel serosa.[34] Furthermore, in real-time near infrared indocyanine fluorescence angiography, the dye can reach the boundaries of ischaemic areas by capillary flow diffusion over time, and therefore the perfused zone may be overestimated. However, only SDF-imaging provides information on how many vessels are perfused, the quality of the flow and whether there are non-perfused areas next to the well-perfused ones. In a previous study we showed that not total microvessel density, but the functional microvessel density is important in order to assess the microcirculation at the level of the anastomosis for the prevention of anastomotic leakage.[35] Diller et al. reported similar results in a rat model with no correlation between total microvessel density and anastomotic leakage, but a significant correlation with decreased functional density.[28]

Hence, the ideal device for microvascular bowel assessment would not only be able to measure microvascular density or the presence of flow or no flow, but also the quality of the microcirculation, by quantifying convection and diffusion. Major advantage of SDFimaging taking these requirements into account is the microscopic visual inspection of the microcirculation thereby giving quality information on convection, diffusion and heterogeneity of flow. There were some difficulties in obtaining bowel serosal images with the SDF, which were less seen sublingually. Most of these difficulties were due to problems with image stabilization. The SDF-device illumination intensity and image focus are operated by a manual dial on the device itself, making it difficult to adjust illumination and focus while keeping the image of interest still, regardless of operator stability. The weight of the device (±0,5 kg), bowel peristalsis and conduction of the movement by respiration and heart activity through the intestinal package were contributing factors to decreased image stability. These factors resulted in a difference in time to image acquisition, loss of pixels due to image drift and a lower success percentage compared to the sublingual assessment. In order for SDF microvascular imaging to be a contributor to the assessment of serosal microcirculation and ultimately improved anastomotic healing, these problems need to be overcome. Within our research group several options to overcome these problems were proposed. One of these solutions is the use of an image stabilizer previously describe by Balestra et al.[36] This image stabilizer(IAS) is a stainless steel ring which fits snuggly around the tip of the SDFprobe and creates adhesion with the area of interest by applied mild negative pressure. The IAS was validated for sublingual use and no effect was reported on the sublingual microcirculation or damage to mucosa. Both axial and lateral stability was improved and thereby the risk of pressure artifacts also reduced. Another solution is the development of a third generation hand-held bedside imaging device, the Cytocam or Incident Dark Field imaging (Cytocam-IDF, Braedius Medical, Huizen, The Netherlands).[37] This is a lightweight (120g) computer controlled imaging sensor-based hand-held microscope, which is smaller than the SDF(MicroScan), pen-like and held as such. The image focus and illumination are controlled on a computer that is connected to the Cytocam-IDF, thereby eliminating motion when adjusting these and may cause less image movement. In this feasibility study we only investigated the serosal microcirculation, but the role of the mucosal microcirculation for anastomotic healing is not totally clear. There are studies which suggest that by measuring the serosal microcirculation anastomotic leakage during colorectal surgery can be predicted[10,31-34], but other research shows that mucosal microcirculation is much more vulnerable for microvascular and hemodynamic alterations. Animal studies during progressive bleeding show more severe microvascular alterations in the ileal mucosa compared to the ileal serosal microcirculation. Recovery after endotoxemic shock also showed a lagging recovery of the mucosal microcirculation compared to serosal and sublingual microcirculation.[38,39] Boerma et al.

have also found similar results comparing ileal mucosa to sublingual microcirculation in patients with abdominal sepsis and an intestinal stoma. Microvascular indices were dissociated between sublingual and ilial mucosa, only mucosal measurements were related to outcome.[20] The role and importance of the mucosal microcirculation in anastomotic healing and its relation to serosal microcirculation should be taken into account in future research in anastomotic healing. There are obvious and significant difference seen in the scored microvascular parameters and in our opinion these differences in the TVD and PVD are explained by anatomy. The significant difference in PPV may be because of procedural and patient factors. First is to be mentioned that a normal sublingual MFI and PPV is considered >2.7 and >90%, respectively and our sublingual measurements are conform in other studies.[9,24,40,41] Most measurements were done on manipulated parts of bowel usually either before or just after creation of a bowel anastomosis. None of the measurements were done directly on the anastomosis, but microvascular alterations due to manipulation could have caused this slight difference in PPV. Furthermore, eight patients received low dose norepinephrine which could affect the microcirculation of the bowel, but also the sublingual. The difficulties in images stability mentioned could also have contributed to the difference in PPV because of too much traction or pressure, but impaired large vessel perfusion is a good indicator for too much pressure. In case of pressure artifacts the camera surface pressure was lowered until sufficient improvement of large vessel perfusion or measurements were excluded, three measurements were excluded for this reason. During measurements the bowel was held in the hands of the surgeon in the abdominal cavity in its most natural position, without traction on or lifting of the bowel. The only moment when the serosal side of the bowel is accessible in laparoscopic surgery for microcirculatory assessment is during extracorporeal creation of the anastomosis, six patient underwent such laparoscopic low anterior or sigmoid resection. Obviously, traction can then not always be avoided and the only part of the bowel accessible surely is manipulated. All these factors may affect the normal values of these microcirculatory bowel serosal measurements in this study. As a feasibility study producing normal values was not the primary end point and future research should be aimed at describing the indices of microcirculation during different hemodynamic and pathophysiological conditions.

In conclusion, Sidestream Dark Field imaging is a promising technique for bowel microcirculatory visualization and assessment. It is comparable to sublingual assessment and the analysis produces similar outcome with slightly differed anatomical features. In future research and clinical practice it could contribute in understanding and assessment of anastomotic healing, if the problems of image stability and extensive off-line analysis are overcome.

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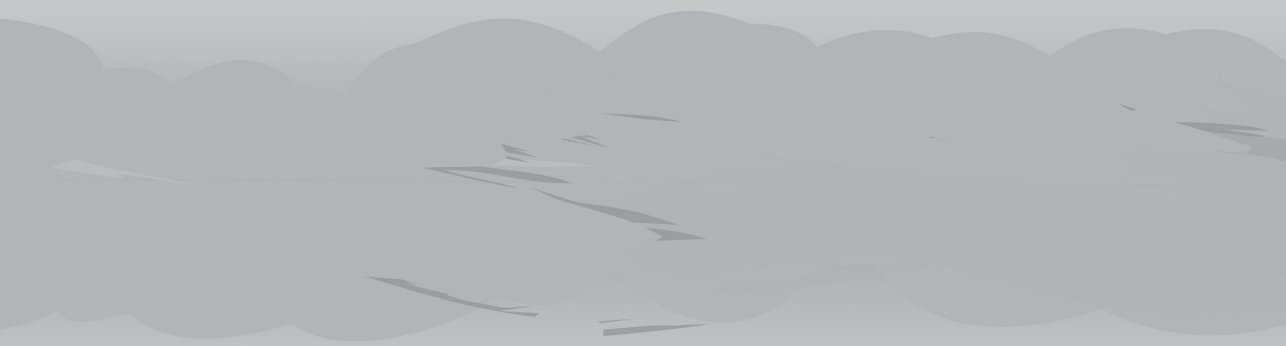
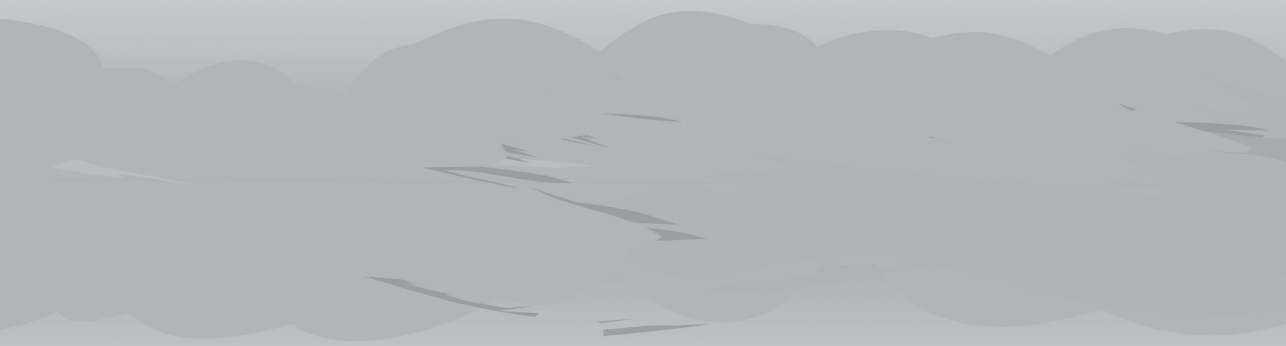


PART III

Early detection of postoperative complications after colorectal surgery



Chapter 6

Systematic review on the value of CT scanning in the diagnosis of anastomotic leakage after colorectal surgery

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ABSTRACT

Background

Timely diagnosis of anastomotic leakage after colorectal surgery and adequate treatment is important to reduce morbidity and mortality. Abdominal computed tomography (CT) scanning is the diagnostic tool of preference, but its value may be questionable in the early postoperative period. The accuracy of CT scanning for the detection of anastomotic leakage and its role in timing of intervention was evaluated.

Methods

A systematic literature search was performed. Relevant publications were identified from four electronic databases between 1990 and 2011. Inclusion criteria were human studies, studies published in English or Dutch, colorectal surgery with primary anastomosis, and abdominal CT scan with reported outcome for the detection of anastomotic leakage. Exclusion criteria were cohort of fewer than five patients, other gastrointestinal surgery, no anastomosis, and radiological imaging other than CT.

Results

Eight studies, including 221 abdominal CT scans, fulfilled the inclusion criteria. Overall, the methodological quality of the studies was poor. The overall sensitivity of CT scanning to diagnose leakage was 0.68 (95% confidence interval 0.59–0.75) for colonic resection. Data on the sequelae of false-negative CT scanning was not available.

Conclusion

There is limited good-quality evidence to determine the value of CT scans in the detection of anastomotic leakage. To prevent delay in diagnosis and appropriate treatment of anastomotic leakage, the relatively low sensitivity of CT scanning must be taken into account.

INTRODUCTION

The most feared complication after colorectal surgery is anastomotic leakage. This severe complication can be life-threatening if not rapidly and correctly diagnosed and treated. Emergent reoperation is generally necessary. Mortality rates due to anastomotic leakage are ranging from 7.5 to 39% in the literature.[1-9] In an effort to reduce leakage rates many studies have focused on identifying patients at risk for the postoperative development of anastomotic leakage.[2-6,10-15] But despite these high numbers of studies concentrating on preventing anastomotic leakage, the reported incidence remains as high as 28%.[1-8,10-12,16-26] Given the fact that we have not yet achieved full understanding of the pathophysiology of anastomotic failure, the issue of adequate and timely diagnosis of leakage needs attention.

Anastomotic leaks may present abruptly and with very clear clinical signs not requiring diagnostic imaging. The majority of patients, however, present with more subtle and confusing symptomatology. When these subtle symptoms are added up into a clinical probability score of anastomotic leakage the delay in diagnosis may be reduced.[9] Still, the actual diagnosis of leakage often requires further non-invasive studies. The preferred imaging tool for the detection of anastomotic leakage is abdominal computed tomography (CT), because it provides a more precise image of the anastomosis and peri-anastomotic structures compared with conventional radiology. In addition, CT scanning may also be useful in detecting other postoperative sequelae, such as intra-abdominal abscesses or haematoma's mimicking the symptoms of leakage.[6,16,27] Conversely, the results of CT scanning can be inconclusive leading to false-positive or false-negative outcomes with a subsequent delay in diagnosis or unnecessary reoperations in patients without anastomotic leaks.[28]

The primary aim of this systematic review was to determine the accuracy of postoperative abdominal CT scans in detecting anastomotic leakage after colorectal surgery in patients suspicious of leakage. The role of CT scanning in the timing and outcome of intervention was evaluated.

MATERIAL AND METHODS

The standard guidelines outlined in the Cochrane Handbook for Systematic Interventions (version 5.1.0) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were used for this review.[29,30]

Search strategy and study selection

A systematic search for all English and Dutch language literature from 1 January 1990 to 31 December 2011 was performed in four biomedical bibliographical databases: Embase, MEDLINE, Pubmed and the Cochrane Library. Search terms in Embase and MEDLINE were all textwords on 'colorectal surgery' AND 'CT scan' AND 'anastomotic leakage' in title, abstract and medical subject heading (MeSH). The Cochrane Library search terms were restricted to title, abstract and keywords.

All titles and abstracts of studies identified were screened independently by three authors (DB, VNNK and NT) to assess eligibility. All cross-references were screened for potentially relevant studies not identified by the initial literature search.

Inclusion criteria were: human studies; studies published in English or Dutch; any colorectal surgery with primary anastomosis; abdominal CT scan as diagnostic tool in the postoperative period for the detection of anastomotic leakage; reported outcome of abdominal CT scan.

Exclusion criteria were: small cohort studies (<5 patients; case reports); study protocols; gastrointestinal surgery other than colorectal surgery or without anastomosis, radiological imaging other than CT scan. Any duplicate studies were excluded. When multiple publications from institutions reporting the same cohort were found, only the most recent and complete articles were included. The flow chart of study selection is summarized in figure 1. The final decision on eligibility was reached by consensus.

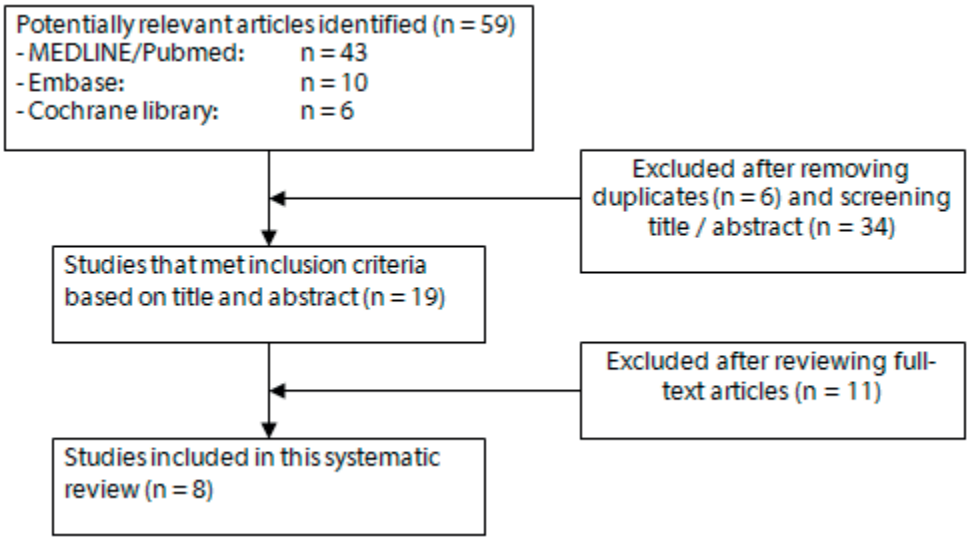

Figure 1. Flow chart of the study selection according to the PRISMA Statement[30]

Quality of included studies

The methodological quality of each included study was assessed using the Oxford Centre for Evidence-Based Medicine levels of evidence.[31] Non-randomized trials were analyzed for evidence of bias, in particular selection, observer and reporting bias. All assessments and grading were undertaken independently by two reviewers, with disagreement resolved by discussion and consensus with the third author.

Data extraction

The following data if available, were extracted from the included studies: study details, number of patients who underwent colorectal surgery, surgical procedure, definition of anastomotic leak, incidence of anastomotic leak, indication and timing of diagnostic examination and report, timing of diagnosis, timing of (re)intervention, delay in diagnosis and intervention after a positive or negative outcome of a CT scan, sensitivity, specificity, accuracy, false-positive and false-negative results of abdominal CT scan in diagnosing postoperative anastomotic leakage, and mortality.

Data analysis

All available data were extracted and pooled into a separate database. Sensitivity, specificity, positive and negative predictive value with 95% confidence intervals were calculated whenever possible. The data were analyzed with SPSS statistical software (SPSS Statistics Version 17.0, Inc., Chicago, Illinois, USA). Meta-analysis was not performed because of the heterogeneity between studies in terms of design and data reporting.

RESULTS

After exclusion of overlapping studies 53 abstracts were screened (figure 1). Of these, 34 were excluded for the following reasons: articles not written in English or Dutch (8), case reports (4), study protocol (1), animal studies (3), no colorectal surgery or abdominal CT scan (16), no full text available (2) were excluded.

The full text of 19 remaining articles was analyzed, of which eleven articles were excluded for the following reasons: preoperative abdominal or pelvic CT scans (2)[32,33]; no available data on abdominal or pelvic CT scans (6)[8,21,25,34-36]; imaging studies for the diagnosis of other complications than anastomotic leakage (2)[37,38]; other procedure than colorectal surgery (1).[39] The remaining eight articles were included in the present systematic review.[6,16,23,24,27,28,40,41] Three studies were prospective non-controlled case series and five

were retrospective non-controlled case series. Characteristics of the included studies are summarized in table 1a and 1b.

Table 1a. Characteristics of included studies

Reference	Year	Country	Period	Design	Sample size
Alves *et al.*[6]	1999	France	1990-1997	R	655
Eckmann *et al.*[27]	2004	Germany	1992-2000	R	306
Nicksa *et al.*[24]	2004	USA	1997-2004	R	36
Nesbakken *et al.*[23]	2005	Norway	4 years	P	56
Hyman *et al.*[16]	2007	United Kingdom	1995-2004	P	1031*
Doeksen *et al.*[40]	2008	Nether-lands	2000-2005	R	429
Khoury *et al.*[28]	2009	Israel	1998-2006	R	32*
Kanellos *et al.*[41]	2010	Greece	1990-2009	R	170

* Only colorectal patients; AL, anastomotic leakage; R, retrospective; P, prospective.

Table 1b. Characteristics of included studies

Reference	Definition AL	AL confirmed by	Incidence AL (all pt)	Imaging study
Alves *et al.*[6]	Yes	Reoperation.	6% (39/655)	Abd. CT scan (3); water soluble contrast radiography (18); both (6).
Eckmann *et al.*[27]	Yes	CT scan, sigmoidoscopy, contrast enema radiography.	9.8% (30/306)	Abd./ pelvic CT scan, sigmoidoscopy, contrast enema radiography.
Nicksa *et al.*[24]	Yes	Relaparotomy.	100% (all pt)	Abd. CT scan (27), water soluble contrast radiography (18).
Nesbakken *et al.*[23]	Yes	Reoperation, endoscopy (>3 months)	17.9% (10/56)	Abd. CT scan (47), contrast radiopgraphy (56), endoscopy.
Hyman *et al.*[16]	Yes	Imaging, reoperation.	3.1% (31/1013)	Abd. CT scan (19), contrast enema radiography (10).
Doeksen *et al.*[40]	No	Reoperation, clinical (transanal drainage of pus, palpable defect).	15.9% (68/429)	Abd. CT scan (27), water soluble contrast radiography (40), both (24).
Khoury *et al.*[28]	Yes	Reoperation.	100% (all pt)	Abd.CT scan (24).
Kanellos *et al.*[41]	Yes	CT scan, surgery.	8.2% (14/170)	Abd./pelvic CT scan (14).

AL, anastomotic leakage; CT, computed tomography; Abd, abdominal; pt, patients.

Quality of included studies

All included studies were observational studies. Based on the Oxford Centre for Evidence-Based Medicine these studies were graded as level 3 or 4. Most studies included small

numbers of CT scans. In six studies a total of 30 or fewer CT scans were performed. Only two larger studies described the results of false-positive, false-negative and true-negative CT scans[19,39] Definitions to define anastomotic leakage, both clinically and radiologically, varied widely between studies, making pooling of data impossible.

Patient characteristics

The eight studies included a total of 2715 patients who underwent colorectal surgery. The incidence of anastomotic leakage could be extracted from six studies and ranged from 3.1% to 17.9% with an overall incidence of 7.3% (192/2629).[6,16,23,28,40,41] In the remaining two studies only patients with anastomotic leakage were included and were therefore excluded from calculation of the overall incidence.[24,27] The majority of patients were operated for malignant disease. Five studies included different types of colectomies[6,16,24,28,40], whereas in three studies all patients underwent (lower) anterior resection for sigmoid or rectal cancer.[23,27,41] Patient characteristics and procedures are summarized in table 2a and 2b.

Table 2a. Patient characteristics

Reference	Male/ Female	Age	Elective/ urgent	Aetiology (all patients)
Alves *et al.*[6]	NR	NR	Elective	Colorectal carcinoma, Crohn's disease, ulcerative colitis, diverticulitis, benign polyp, miscellaneous.
Eckmann *et al.*[27]	Male (67%); Female (33%)	Mn 67 yrs	Elective	Rectal cancer
Nicksa *et al.*[24]	Male (50%); Female (50%)	Mn 55 yrs (22-82)	NR	Colorectal cancer, diverticulitis, ulcerative colitis, Crohn's disease, other.
Nesbakken *et al.*[23]	NR	NR	NR	Rectal carcinoma.
Hyman *et al.*[16]	NR	NR	NR	NR
Doeksen *et al.*[40]	NR	NR	NR	NR
Khoury *et al.*[28]	NR	NR	NR	Gastro-intestinal tract surgery and postoperative anastomotic leakage.
Kanellos *et al.*[41]	Male (79%); Female (21%)	Mn 66 yrs (54-78)	Elective / urgent	Rectal cancer

Age in mean (Mn) or median (Md) years (yrs) with range. NR, not reported.

Postoperative results of CT scan

A total of 221 abdominal or pelvic CT scans were performed to detect postoperative anastomotic leakage. Indication for the CT scan was clinical suspicion of anastomotic leakage in all but one study; in this study CT scanning was routinely performed in one study on postoperative day 6-10.[23] Table 3 (a and b) shows the outcomes of postoperative CT

Table 2b. Patient characteristics

Reference	Surgical procedure (all patients)	Anastomosis	Hand-sewn vs stapled	Diverting stoma
Alves *et al.*[6]	Right or left hemicolectomy, transverse or (sub) total colectomy, anterior resection.	E-E, E-S, S-E, S-S.	Hand-sewn; stapled.	No
Eckmann *et al.*[27]	Low anterior resection	E-E	Stapled	No
Nicksa *et al.*[24]	Reoperation for LGAL (right or left hemicolectomy, ileocolectomy, ileostomy closure, sigmoidectomy, low anterior resection).	NR	NR	No
Nesbakken *et al.*[23]	TME, PME.	E-E, S-E (reservoir)	NR	Yes (45%).
Hyman *et al.*[16]	Anastomosis: Colocolic, ileocolic, colorectal, ileorectal, ileoanal, coloanal.	NR	NR	No
Doeksen *et al.*[40]	Ileocolonic resection, right or left hemicolectomy, transverse or sigmoidal or (sub)total colectomy, low anterior resection, restore colonic continuity.	E-E, E-S, S-E, S-S.	NR	NR
Khoury *et al.*[28]	Right hemicolectomy, left hemicolectomy/ sigmoidectomy, (sub)total colectomy, rectal resection.	NR	NR	NR
Kanellos *et al.*[41]	Low anterior resection	NR	Hand-sewn; stapled.	NR

NR, not reported; E-E, end-to-end; E-S, end-to-side; S-E, side-to-end; S-S, side-to-side; vs, versus; AL, anastomotic leakage; pt, patients; TME, total mesorectal excision; PME, proximal mesorectal excision; LGAL, lower gastrointestinal anastomotic leak.

scans. The radiological criteria for the CT diagnosis of anastomotic leakage were not specified[6,16,27,41] or varied widely[23,24,28] (table 4). Likewise, the clinical definitions of anastomotic leakage were not-mentioned or differed greatly (table 5).

Accuracy of postoperative abdominal CT scans

The overall sensitivity of CT scanning to detect anastomotic leakage, calculated for all studies combined, was 0.68 (95% CI 0.59-0.75). The specificity could be calculated from two studies only, because these studies reported false positive results of the CT scanning at relaparotomy, and was 1.00 (95% CI 0.89-1.00) and 0.78 (95% CI 0.57-0.91), respectively.[23,40] When analyzing the three studies with only rectal resections separately[23,27,41], the sensitivity of CT scanning with administration of rectal contrast for the detection of anastomotic leakage was 0.92 (95% CI 0.80-0.97) with 47 true-positive and 4 false-negative CT outcomes.

Table 3a. Results postoperative CT scans

Reference	Included CT scans	Indication CT scan	Contrast	Time interval prim. operation - CT scan	Time interval CT scan - re-intervention
Alves *et al.*[6]	9	Clinical	NR	Mn 8 days (4-25) *	No delay
Eckmann *et al.*[27]	30	Clinical	Rectal	NR	NR
Nicksa *et al.*[24]	27†	Clinical	Oral, rectal, intravenous	NR	Mn postoperative day 10,1 (2-50).
Nesbakken *et al.*[23]	47	Clinical; routinely day 6-10	Gastrografin enema	NR	NR
Hyman *et al.*[16]	19	Clinical	NR	Mn 16 days *	NR
Doeksen *et al.*[40]	51	Clinical	Oral, intravenous	Mn 7 days (1-49) *	< 24 hr with positive CT scan
Khoury *et al.*[28]	24	Clinical	Oral, rectal	NR	< 72 hr after CT scan; Mn post-operative day 7,3 (SD 4,4).
Kanellos *et al.*[41]	14	Clinical	Rectal	NR	Mn postoperative day 6,8 (5-8).

CT, computed tomography; NR, not reported; Mn, mean; SD, standard deviation. Time interval in days (range).
† Total number of positive CT scans and high probability CT scans for anastomotic leakage or negative CT scans and low probability CT scans for anastomotic leakage and calculated sensitivity.
* Both CT scan and water-soluble contrast radiography.

Table 3b. Results postoperative CT scans

Reference	Anastomotic leakage and pos. CT scan	Anastomotic leakage and neg. CT scan	Sensitivity (CI 95%)	Other results
Alves *et al.*[6]	8	1	0.89 (0.51-0.99)	No
Eckmann *et al.*[27]	29	1	0.97 (0.81-0.99)	No
Nicksa *et al.*[24]	4 (13†)	23 (14†)	0.15 (0.05-0.35) † 0.48 (0.29-0.68)	No
Nesbakken *et al.*[23]	4	3	0.57 (0.20-0.88)	Specificity: 1.00 (CI 0.89-1.00) PPV: 1.00 (CI 0.40-1.00) NPV: 0.96 (CI 0.80-0.98) Accuracy: 0.94
Hyman *et al.*[16]	17	2	0.89 (0.67-0.98)	No
Doeksen *et al.*[40]	13	11	0.54 (0.34-0.74)	Specificity: 0.78 (CI 0.57-0.91) PPV: 0.68 (CI 0.44-0.86) NPV: 0.66 (CI 0.49-0.84) Interobserver variability: 10%
Khoury *et al.*[28]	4 (13†)	3 (11†)	0.54 (0.20-0.88) † 0.57 (0.33-0.74)	No
Kanellos *et al.*[41]	14	0	1.00 (0.73-1.00)	No

CT, computed tomography; PPV, positive predictive value; NPV, negative predictive value; CI, 95% confidence interval.
† Total number of positive CT scans and high probability CT scans for anastomotic leakage or negative CT scans and low probability CT scans for anastomotic leakage and calculated sensitivity.

Delay of adequate intervention after false negative CT scans

Reviewing and pooling the data of the eight included articles, only one study[28] reported on the delay of treatment after false negative CT scanning (i.e. over 24 hours of delay in 24.4% of the patients). However, the consequences of this delay in appropriate treatment were not addressed in this study.

Table 4. Radiological criteria for the CT diagnosis of anastomotic leakage

Reference	Positive for AL	High probability	Low probability	Negative / normal
Alves *et al.*[6]	NR	NR	NR	NR
Eckmann *et al.*[27]	NR	NR	NR	NR
Nicksa *et al.*[24]	Extraluminal contrast or clear extravasation from the suture line.	Large amounts of free intraperitoneal fluid or extraluminal free air.*	NR	NR
Nesbakken *et al.*[23]	Extraluminal collection of contrast medium, presence and location of air bubbles in the pelvis.	NR	NR	NR
Hyman *et al.*[16]	NR	NR	NR	NR
Doeksen *et al.*[40]	Contrast outside bowel lumen, perianastomotic fluid collections, air directly near the anastomosis, pneumoperitoneum > 1 wk postoperatively.	NR	NR	NR
Khoury *et al.*[28]	Extraluminal contrast.	Large amount of free intraperitoneal air or fluid.	Low amount of air or fluid.	No findings.
Kanellos *et al.*[41]	NR	NR	NR	NR

AL, anastomotic leakage; NR, not reported; wk, week. * Described as 'descriptive positive'.

DISCUSSION

Given the widespread use of CT scanning in detecting complications in the postoperative course after colorectal surgery, and given the high numbers of patients undergoing this type of surgery annually worldwide, there is a stunning paucity of data concerning the accuracy of CT scanning in the detection of anastomotic leakage following colorectal surgery. In the present systematic review only eight studies, all of moderate methodological quality were eligible for analysis. Even by combining all 2715 patients in these eight studies, a total number of only 221 abdominal CT scans remain. The calculated overall sensitivity of CT scanning for the detection of anastomotic leakage proved to be 0.92 (95% CI 0.80-0.97) after rectal resections and appears to be as low as 0.68 (95% CI 0.59-0.75) after colorectal surgery.

Table 5. Clinical definition of anastomotic leakage

Reference	Consideration or indication of anastomotic leakage	Confirmed by
Alves *et al.*[6]	Clinical: pus or fecal discharge from the drain, pelvic abscess, peritonits, discharge of pus per rectum.	Relaparotomy.
Eckmann *et al.*[27]	Consideration: Pelvic pain, fever or leukocytosis. Indication: Feculent substances from the pelvic drain. Major leaks: peritonitis and septicemia due to leakage, necessary surgical intervention. Minor leaks: small amount of extravasation accompanied by less dramatic clinical signs, no sepsis. Treated with transanal lavage or CT-guided abscess drainage.	Abdominal and pelvic CT scan with rectal contrast enema, contrast enema radiography, flexible sigmoidoscopy.
Nicksa *et al.*[24]	Clinical anastomotic leak confirmed at relaparotomy.	Relaparotomy.
Nesbakken *et al.*[23]	Clinical and imaging (the presence of an extraluminal collection of contrast medium, air bubbles in the pelvis). Subclinical leak: an asymptomatic leak during hospital stay.	Relaparotomy, endoscopy 3 months after surgery.
Hyman *et al.*[16]	Clinical and imaging. Including postoperative fistulas communicating with the surgical anastomosis and postoperative abscesses with extravasation of enteric contrast, significant peri-anastomotic air, communication with the anastomosis.	Imaging and surgery.
Doeksen *et al.*[40]	Clinical.	Relaparotomy, transanal drainage of pus or as palpable defect identified at digital examination.
Khoury *et al.*[28]	Enteral content in the peritoneal cavity combined with documented anastomotic dehiscence or missed enteral injury, necessary surgical intervention.	Surgery.
Kanellos *et al.*[41]	Pelvic pain, unexplained pyrexia, tachycardia, leucocytosis, symptoms simulating an acute cardiorespiratory event, fecal discharge from the drain, septicemia, peritonitis. Major leaks: peritonitis, septicemia, necessary surgical intervention. Minor leaks: small amount of extravasations accompanied by mild clinical signs, no sepsis, conservative treatment.	Abdominal and pelvic CT scan with rectal contrast enema or surgery.

Although CT scanning has an undisputed role in the diagnosis of major sequelae following abdominal surgery such as detection of fluid collections, intra-abdominal abscesses or hematoma's[6,27], the accuracy of abdominal CT scanning in the diagnosis of anastomotic leakage was found to be surprisingly low. Additionally, the accuracy of CT scanning in the early postoperative period, within the first few days after surgery may even be lower when compared to a CT scan more than a week after surgery. Two studies by DuBrow et al and Matthiessen et al showed that patients with and without anastomotic leakage have comparable postoperative CT-features, especially in the early postoperative period.[35,43] Large air-fluid collections, anterior displacement of the rectum and extravasation of enteral contrast material ("double rectum sign") are CT signs of failure of the anastomosis[43], but

accumulation of reactive peritoneal effusion and pneumoperitoneum are also common findings following colorectal surgery.[35,44] This indicates that the timing of CT scanning may influence the accuracy in detecting anastomotic leakage.

The documented delay of re-intervention in patients with a false-negative CT scan is, notwithstanding the varying quality of the studies, most relevant and worrisome and constitutes a revolving and daily challenge for the clinician.[28,34,40] It seems appropriate to rephrase the question of the accuracy of CT scanning into 'what should be the clinical consequence of a negative CT scan in the patient suspected of anastomotic leakage'. It is imperative to know how to increase the probability of a suspected anastomotic leak when CT-outcomes are insufficient. Therefore the following four issues need elaboration.

First: What is the additional value of clinical parameters when combined with findings of abdominal CT scans? Several clinical factors associated with an increased risk for anastomotic leakage have been described in the literature, including pelvic pain, fever, tachycardia, oliguria, transit disturbances, increased C-reactive protein (CRP), leukocytosis, renal failure and large amounts of abdominal drain fluid.[6,27,34,35,41] A variable combination of these parameters is associated with an increased likelihood of anastomotic leaks.[6,34] A scoring system combining both clinical and radiological criteria for the detection of anastomotic leakage does not yet exist, but may be helpful in increasing the accuracy of CT scanning in these patients.

Second: In case of a negative CT scan, should we perform other, additional radiological imaging, i.e. contrast studies? Reported sensitivity and specificity figures of contrast studies vary, ranging from superior[24,40] to inferior[6,16] to similar to abdominal CT scans.[23,27] Possibly

Third: Should we repeat abdominal CT scans? Matthiessen et al demonstrated that over time peri-anastomotic fluid increased in patients with anastomotic leakage, as demonstrated on repeated CT scan seven days after surgery.[35] The fact that timing of CT may be an important factor in the accuracy of imaging in the diagnosis of anastomotic leakage has also been suggested by others.[40,42] However, repeated CT scanning is only an option if the clinical condition of that individual patient would allow a delay in diagnosis and subsequent treatment.

Finally: Should we perform relaparotomy anyway in a patient with high clinical suspicion of anastomotic leakage and negative imaging? Moreover, should we not waste time by arranging, performing and interpreting a CT scan? Doeksen et al demonstrated that anas-

tomotic leakage was found in 52% of the patients who underwent relaparotomy despite a negative radiological examination.[40] This means that in one of two patients with the clinical suspicion of an anastomotic leak and negative imaging, anastomotic leakage may be present. Clinical decision remains of utmost importance in the individual patient and should therefore not depend on one specific clinical or additional diagnostic factor. The pre-test chance of the presence of anastomotic leakage based on a combination of multiple parameters may help in adequate decision making. Watchful waiting with the risk of higher morbidity and mortality by delaying the diagnosis when anastomotic leakage is present should be outweighed against the morbidity of a relaparotomy.

A limitation of the present systematic review is that pooling of data was problematic for several reasons. First, data reported between studies varied widely. Second, the studies reviewed included only a small number of patients. In addition, patient populations between studies were heterogeneous. Third, the gold standard (i.e. relaparotomy) was, as expected, not routinely performed in all studies. Finally, a wide variety of clinical and radiological criteria were used to define anastomotic leakage. For instance, the lowest sensitivity of CT scanning (0.15) was observed in a study by Nicksa et al who used strict criteria to define anastomotic leakage[24]; after reviewing their 'negative CT scans' when using other criteria for anastomotic leakage (large amounts of fluid or air in the peritoneal cavity, but without extravasation of contrast), their sensitivity of CT scanning increased and tripled up to 0.48. Despite the fact that a standardized definition for anastomotic leakage was proposed by the UK Surgical Infection Study Group (SISG) in 1991[42], a review by Bruce et al ten years later (2001) still identified 29 different definitions of anastomotic leakage after lower gastrointestinal surgery.[26] This is in accordance with our findings because none on the studies included used the same definition. Therefore, a plea could be made for an update of the standardized definition for anastomotic leakage using well-defined clinical and radiological criteria which should then be adhered to in future clinical trial and reports. In light of all the limitations mentioned, the outcome of this systematic review should be interpreted with caution.

CONCLUSION

In conclusion, timely and correct diagnosis and treatment of anastomotic dehiscence after colorectal surgery remains to be a major challenge. We should be aware of the little and poor quality evidence concerning the value of the CT scan in diagnosing this most important and feared complication. Despite, the available evidence shows a low sensitivity. In order to come to a unified reporting of outcome, we need standardized clinical and

radiological criteria to define anastomotic leakage. Results of future well designed and large prospective studies should be awaited before any harsh conclusions on the accuracy of CT scanning for diagnosing anastomotic leakage can be drawn. Until then, a negative CT scan does not rule out anastomotic dehiscence and, in our opinion, watchful clinical monitoring of the patient is as valuable as diagnostic imaging studies in the proper management of this severe complication.

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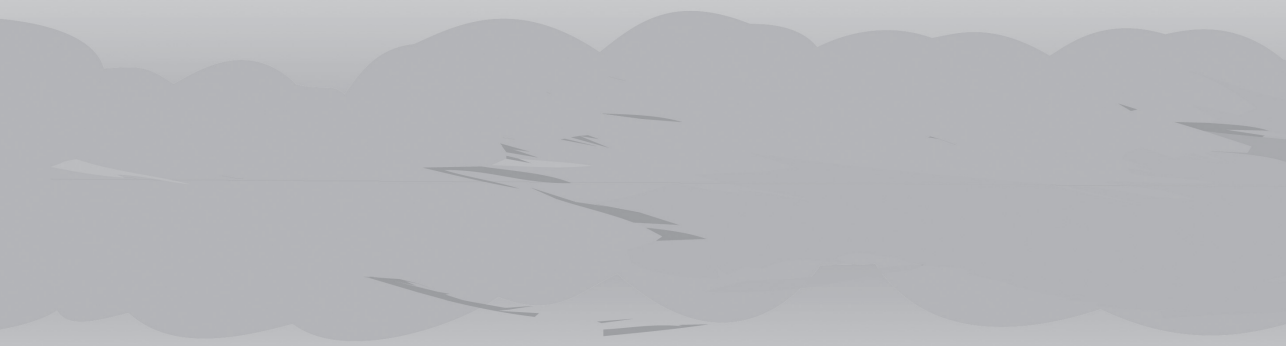

Chapter 7

Beware of false-negative CT-scan for anastomotic leakage after colonic surgery

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ABSTRACT

Background

Anastomotic leakage is one of the most life-threatening complications after colonic surgery. Correct diagnosis and treatment is important to reduce morbidity and mortality. An abdominal CT scan is one of the main diagnostic tools in diagnosing anastomotic leaks. The aim of this study was to examine the accuracy of abdominal CT scanning to detect anastomotic leakage and to evaluate the consequences of a false negative CT outcome.

Methods

All consecutive patients who underwent colonic resection for malignant disease between 2009 and 2011 or for benign disease in 2010 were reviewed. Patients in whom a postoperative abdominal CT scan was performed to detect anastomotic leakage were included.

Results

In 97 of 524 patients who underwent colonic surgery, an abdominal CT scan was performed for the suspicion of anastomotic leakage. Overall leakage rate was 10.9% (n=57). Mortality rate after leakage was 21.1% (n=12). Results from all abdominal CT scans revealed an overall sensitivity of 0.59 (95% CI 0.43-0.73), a specificity of 0.88 (95% CI 0.75-0.95), positive predictive value 0.82 (95% CI 0.64-0.92), negative predictive value 0.70 (95% CI 0.57-0.81) and an accuracy of 74%. Delayed reintervention for anastomotic leakage due to a false negative CT outcome resulted in death in 62.5% (n=5).

Conclusion

The sensitivity of abdominal CT scanning after colonic surgery is relatively low. A negative CT scan does not rule out anastomotic leakage. Even with a negative CT scan, we should remain equally alert at clinical deterioration as an argument for timely intervention.

INTRODUCTION

Anastomotic leakage is a severe and life-threatening complication after colonic surgery. The incidence ranges from 1% to 28%.[1-15] Mortality after anastomotic leakage is high and a rate up to 39% is reported in the literature.[2,4,8,13-17] Rapid diagnosis and treatment is of utmost importance to reduce morbidity and mortality.[17] First and foremost, the deterioration of the patient's clinical condition is leading in the suspicion of anastomotic leakage. In outspoken cases the decision to reoperate can easily be made clinically, without additional radiological imaging modalities. The challenge is to identify leakage in those cases with more subtle and confusing signs and symptoms in the early postoperative period. Clinical parameters as a primary diagnostic tool to detect anastomotic leakage have a low sensitivity.[7,14,18,19] Several studies have focussed on clinical scoring systems for the diagnosis of anastomotic leakage, but most of these scores have not been validated.[20,21] Also 'trigger systems', i.e. early warning scores and medical emergency teams, have been introduced worldwide for rapid identification of surgical and non-surgical patients with deteriorating clinical conditions.[22-24] These scoring systems have not yet been introduced for the identification of patients with anastomotic leakage. Until today uniform parameters for the early detection of patients with anastomotic leakage are lacking. Radiological imaging may be of help when clinical parameters are considered inconclusive. It is debatable which imaging modality is superior in detecting anastomotic leakage, but CT scanning with enteral contrast is considered the gold standard.[3,14,18,19,25,26] However, literature of the value of CT scanning is limited.[27] Also, little has been reported about the consequences of a false negative CT scan.

In this study we aimed to determine the accuracy of abdominal CT scans in the detection of anastomotic leakage after colorectal surgery in a large group of patients and we analyzed the clinical consequences of false negative imaging.

MATERIAL AND METHODS

All consecutive patients who underwent elective or emergency colonic surgery with primary anastomosis for malignant disease between January 2009 and December 2011 or for benign disease in 2010 were retrospectively analyzed. Patients with rectal anastomosis were excluded from this study. All patients for whom a postoperative abdominal CT scan was performed for the suspicion of anastomotic leakage were included in this study. The early warning score (respiratory rate, pulse rate, systolic blood pressure, temperature, urine production and neurologic status)[23], other clinical parameters, timing and indication of the CT scan, radiological features, interval between CT scan until treatment, reintervention, presence of anastomotic leakage and the clinical outcome were assessed.

CT imaging was performed on a sixteen and a two hundred fifty-six slice-MDCT scanner (Philips, Netherlands) with a slice thickness of algorithm of 3-5 mm with axial and coronal reconstructions. Intravenous contrast (100 ml of iobitridol, Xenetix 300, Guerbet Nederland BV), was given in all patients, excluding those with renal failure or proven allergy. Oral contrast (20 ml iobitridol 300 mg I/ml, Guerbet, diluted in 1 l of tapwater) was given in all patients unless there were signs of ileus. In most patients with signs of a paralytic ileus, a nasogastric tube combined with a feeding tube in the small intestine was placed. The feeding tube in the small intestine was used to give oral contrast. Rectal contrast was not routinely given in patients after colonic resections. CT scans were reviewed by experienced radiologists or radiology residents, supervised at all times. For this study, we used the radiology reports as given at the time. All patients completed follow-up for at least 30 days after primary surgery.

Anastomotic leakage was defined as anastomotic dehiscence visualized at relaparotomy or endoscopy or percutaneous or transanal drainage of pus or enteral contents adjacent to the anastomosis. Radiological anastomotic leakage was defined as the presence of extraluminal contrast medium, air bubbles directly near the anastomosis or perianastomotic fluid collections and/ or pneumoperitoneum.

Statistical analysis

All data were pooled into a database. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals and accuracy were calculated. Quantitative data were expressed as number of patients, mean and standard deviation for normal data or median and inter quartile range (IQR) for non-normal data. $P < 0.05$ was used as level of significance. The data were analyzed with SPSS statistical software (SPSS Statistics Version 19.0, Inc., Chicago, Illinois, USA).

RESULTS

Between January 2009 and December 2011 524 consecutive patients underwent colonic surgery with primary anastomosis. The overall leakage rate was 10.9% (n=57), with an overall mortality rate after leakage of 21.1% (n=12). Leakage rate did not differ between open and laparoscopic procedures. There were also no differences between benign and malignant patients. Eleven patients were reoperated within 6 days after initial surgery (IQR 4.5-9.5), without prior CT scan. The main reason to reoperate on these patients was their clinical condition combined with free air under the diaphragm diagnosed on thoracic or abdominal X-ray or percutaneous drainage of enteral contents. Of these 11 patients, one

patient died (9.1%). In 97 patients an abdominal CT scan for the suspicion of anastomotic leakage was performed (table 1). Anastomotic leakage was confirmed at relaparotomy or drainage in 46 of these patients. Clinical parameters at the time of the CT scan are listed in table 2.

Accuracy of CT scan

Sensitivity of the CT scan to demonstrate anastomotic leakage was 0.59 (95% CI 0.43-0.73) and PPV 0.82 (95% CI 0.64-0.92). Specificity was 0.88 (95% CI 0.75-0.95) and NPV 0.70 (95% CI 0.57-0.81) with an accuracy of 74% (table 3).

Outcome of CT scan and subsequent management

CT outcomes were divided into different groups (table 2):

1. CT outcome suggesting anastomotic leakage (n=33);
2. CT outcome negative for anastomotic leakage, but suggesting other complications (n=7);
3. CT outcome negative for anastomotic leakage or other complications (n=57). This group was further divided into: 3a. Patients who underwent immediate reintervention despite negative CT (n=15); and 3b. Patients who (initially) were managed by 'wait and see' (n=42). Clinical condition of patients at the time of CT scanning is depicted in table 2.

Group 1: CT scan suggesting anastomotic leakage

In 33 of 97 patients the CT scan suggested anastomotic leakage. Of these patients, 31 underwent relaparotomy and anastomotic dehiscence was confirmed in 27 patients. Mortality in these 27 patients with anastomotic leakage was 7.4% (n=2). In 2 patients intra-abdominal hematoma without active bleeding was found upon relaparotomy; two patients underwent negative relaparotomy. These four patients all recovered rapidly. The remaining two patients with a positive CT scan were managed expectantly due to improving clinical course and were discharged from the hospital within three days. There was no delay between diagnosis and reoperation in these 31 patients. Median hospital stay after reintervention was 14 days (IQR 9-25).

Group 2: CT scan suggesting other complications

In 7 patients the CT scan suggested other abdominal complications, i.e. massive hematoma, bowel perforation or abscess not adjacent to the anastomosis. Findings upon relaparotomy were intra-abdominal hematoma (n=2), fascia dehiscence (n=1), obstructive ileus (n=1), abscess (n=1) and large bowel perforation (n=2). Mortality rate in these patients was 0%. Median hospital stay after reintervention was 9 days (IQR 7-25).

Table 1. Baseline and operation-related characteristics

	All patients (n = 97)
Age at surgery (years)	67 (59 - 75)
Sex: male (n) / female (n)	52 (53.6%) / 45 (46.4%)
BMI (kg/m^2)	26.6 (24.1-29.1)
ASA-score	2 (2-3)
- ASA 1 (n)	10 (10.3%)
- ASA 2 (n)	59 (60.8%)
- ASA 3 (n)	28 (28.9%)
Pathology	
- Benign (n)	32 (33.0%)
- Malignant (n)	65 (67.0%)
Approach	
- Laparotomy (n)	65 (67.0%)
- Laparoscopic (n)	26 (26.8%)
- Converted (n)	6 (6.2%)
Type of surgery	
- Ileocecal resection	5 (5.2%)
- Right hemicolectomy	45 (46.4%)
- Left hemicolectomy	5 (5.2%)
- Sigmoidal/anterior resection	20 (20.6%)
- (sub)total colectomy	2 (2.1%)
- Restore bowel continuity	13 (13.4%)
- Other	7 (7.2%)
Type of anastomosis (n=90)	
- End to end (n)	1 (1.1%)
- End to side (n)	14 (15.6%)
- Side to end (n)	3 (3.3%)
- Side to side (n)	72 (80.0%)
Suture or stapled	
- Handsutures (n)	21 (21.6%)
- Stapled (n)	45 (46.4%)
- Both (n)	31 (32.0%)
Timing	
- Elective (n)	83 (85.6%)
- Urgent (n)	14 (14.4%)
Protective ileostomy (n)	5 (5.2%)

Values are given as number of patients (n) and percent (%) of group. Age and BMI are expressed in median (inter quartile range). *BMI* body mass index, *ASA* American Society of Anaesthesiologists.

Table 2. Clinical signs, laboratory results at timing of CT scanning and management with clinical outcome

	Group 1. Positive CT outcome (n = 33)	**Group 2. CT outcome suggesting other complication** (n = 7)	**Group 3a. Negative CT outcome and reintervention** (n = 15)	**Group 3b. Negative CT outcome and 'wait-and-see'** (n = 42)
Abdominal pain (n)	20 (60.6%)	4 (57.1%)	12 (80.0%)	25 (59.5%)
Peritoneal tenderness (n)	20 (60.6%)	4 (57.1%)	12 (80.0%)	25 (59.5%)
Fever > 38.5 degrees (n)	12 (36.4%)	1 (14.3%)	4 (26.7%)	4 (9.5%)
C-reactive protein	253 (167 - 341)	195 (35 - 245)	125 (71 - 261)	199 (142 - 276)
- >200 (n)	22 (66.7%)	3 (42.9%)	7 (46.7%)	17 (40.5%)
Leukocyte count[a]	12.8 (7.6 - 15.2)	10.0 (7.1 - 21.4)	11.3 (8.4 - 22.4)	10.0 (6.7 - 14.2)
- ≤ 3.5 / ≥ 13 (n)[a]	15 (45.5%)	3 (42.9%)	7 (50.0%)	15 (38.5%)
Early Warning Score[23]	2 (0 - 3)	1 (0 - 3)	2 (0 - 6)	0 (0 - 1)
Timing of CT scan (days)	5 (4 - 8.5)	10 (7 - 17)	7 (4 - 10)	6 (5 - 14)
Reintervention (n)	31 (93.9%)	7 (100%)	15 (100%)	8 (19.0%)[b]
Timing of reintervention after CT scanning (days)	0 (0 - 0)	0 (0 - 2)	1 (0 - 2)	6 (4 - 16)
Anastomotic leakage (n)	27 (81.8%)	0 (0%)	11 (73.3%)	8 (19.0%)
Mortality rate in leaking patients (n)	2 (7.4%)	-	4 (36.4%)	5 (62.5%)
Hospital stay after reintervention (days)	14 (9 - 25)	9 (7 - 25)	25 (11 - 38)	26 (15 - 33)

Values are given as number of patients (n) and percent (%) of group or median with inter quartile range (IQR). C-reactive protein (mg/L); Leukocyte count $x10^9$/L. The p-value describes the difference between all patients with anastomotic leakage and different CT outcomes.
[a] Data does not add up to 93 because of occasional missing data.
[b] Delayed reintervention

Group 3: CT scan negative for anastomotic leakage or other complications

In 57 patients the CT scan was judged as normal without significant signs of anastomotic dehiscence or other abdominal pathology. Nineteen of these patients were found to have anastomotic leakage despite this negative scan (33.3%). Mortality rate among these 19 patients with leakage was 47.7% (n=9). Fifteen of these 57 patients with a negative CT outcome underwent immediate relaparotomy because of clinical deterioration (group 3a), and the remaining 42 patients were managed by 'wait and see' because of milder clinical symptoms (group 3b). In group 3a, anastomotic leakage was confirmed in 11 of 15 patients; mortality in these patients with leakage was 36.4% (n=4). Median hospital stay after leakage of the survivors was 25 days (IQR 11-38). After negative relaparotomy, 1 patient required antibiotic treatment for pneumonia and the remaining three patients recovered uneventfully.

Table 3. Sensitivity, specificity, positive and negative predictive value

CT-outcome	Anastomotic leakage (n)	No anastomotic leakage (n)	Results (95% CI)
Positive	27	6	Sensitivity: 0.59 (0.43-0.73) Specificity: 0.88 (0.75-0.95)
Negative	19	45	PPV: 0.82 (0.64-0.92) NPV: 0.70 (0.57-0.81)

PPV, positive predictive value; NPV, negative predictive value. Values are given as number of patients (n). Sensitivity, specificity, PPV and NPV are given with 95% CI (confidence interval).

The remaining 42 patients with a negative CT scan were initially managed by 'wait and see' (group 3b). Eight patients in this group were eventually found to suffer from anastomotic leakage, of which 5 patients died (mortality rate 62.5%). In 7 of these 8 patients with leakage a second CT scan was performed: in five patients the CT scan showed minimally increased fluid and air collections directly next to the anastomosis and CT scan was again negative for leakage in two patients. In 2 of the 8 patients with leakage we abstained from reoperation at the time of diagnosis because of a poor clinical status of the patient; the remaining 6 patients underwent relaparotomy on a median of 6 days after the first negative CT scan (IQR 4-16), resulting in prolonged ICU treatment for multiple organ failure in all patients and death in 3 patients. Median hospital stay after leakage of the survivors was 26 days (IQR 15-33). The remaining 34 patients in group 3b recovered rapidly and did not undergo reintervention.

CT features indicating anastomotic leakage

Intra-abdominal free air and localized perianastomotic fluid and air were significantly more frequently observed in patients with anastomotic leakage versus patients without anastomotic leakage. There were no differences in the occurrence of intra-abdominal fluid collections between these two groups, p=0.130 (table 4).

Table 4. Postoperative CT features

	All patients (n = 97)	**No leakage** (n = 51)	**Anastomotic leakage** (n = 46)	**p-value**	**OR (95% CI)**
Intra-abdominal fluid collection	77 (79.4%)	37 (72.5%)	40 (87.0%)	0.130	2.52 (0.88-7.25)
Intra-abdominal free air	48 (49.5%)	14 (27.5%)	34 (73.9%)	< 0.001	7.49 (3.04-18.43)
Peri-anastomotic localized fluid	33 (34.0%)	7 (13.7%)	26 (56.5%)	< 0.001	8.17 (3.04-21.95)
Peri-anastomotic free air	34 (35.1%)	7 (13.7%)	27 (58.7%)	< 0.001	8.93 (3.12-24.04)

Values are given as number of patients (n) and percent (%) of group; OR, odds ratio with 95% confidence interval.

Elective versus emergency surgery

Leakage rates were comparable between patients who underwent elective versus emergency surgery. Sensitivity and specificity of the CT scan were comparable between elective and emergency operated patients: 0.60 (95% CI 0.43-0.75) versus 0.50 (95% CI 0.14-0.86) for sensitivity and 0.88 (95% CI 0.74-0.96) versus 0.88 (95% CI 0.47-0.99) for specificity. PPV was 0.83 (95% CI 0.64-0.94) versus 0.75 (95% CI 0.22-0.99) and NPV 0.70 (95% CI 0.56-0.82) versus 0.70 (95% CI 0.35-0.92) respectively). One out of 14 emergency patients died, CT scan was false negative in this patient (33%). A false negative CT scan for elective patients (n=16) resulted in death in 8 patients (50%).

DISCUSSION

Timely diagnosis of anastomotic leakage after colonic surgery is a daily challenge in surgical practice. Clinical and biochemical parameters and radiologic imaging may help us in detecting anastomotic dehiscence. In this study, with the largest homogeneous group of patients for whom an abdominal CT scan was performed for the suspicion of anastomotic leakage after colonic surgery (n=97), overall sensitivity was as low as 0.59 (95% CI 0.43-0.73). Of all patients with a negative CT scan 33% of the patients eventually appeared to have an anastomotic leakage. Mortality rate due to delay in diagnosis after a false negative CT scan increased to 63% after delayed diagnosis versus less than 10% in patients with a positive CT outcome and immediate intervention.

Abdominal CT scanning undoubtedly has its value in the detection of anastomotic leakage, but sensitivity of CT scanning to detect anastomotic leakage in this study was low. These results are in accordance with a recent review in which we demonstrated that the overall sensitivity calculated from eight different studies with a total number of 221 abdominal CT scans after colorectal surgery was 0.68 (95% CI 0.59-0.75).[27] However, the available literature is limited, includes small numbers of heterogeneous study populations, and different definitions for clinical and radiological anastomotic leakage are used.[3,14,18,19,25-29] Despite the limited quality of the available literature, we all consider CT scanning as an important diagnostic parameter in diagnosing or ruling out anastomotic dehiscence and clinicians tend heavily to rely on its outcome. Previous studies reported that a false negative CT outcome may delay adequate treatment[29,30], but the consequences of a false negative CT scan are not well described. Our study surprisingly demonstrates that we should not only be aware of the low sensitivity of CT (which is almost as reliable as a flip of the coin), but foremost of its limited specificity: a false negative CT scan may delay early diagnosis and thereby adequate treatment, with potentially devastating consequences.

Our results clearly show the difference in clinical decision making after negative CT scanning: immediate reintervention versus 'wait and see'. When re-evaluating the clinical course at time of CT scanning, clinical and vital signs of patients with a negative CT scan who underwent immediate reintervention (group 3a) were worse compared with the mild clinical signs of group 3b ('wait and see'). A false negative CT scan combined with mild clinical symptoms resulted in a 'wait and see' policy (group 3b) and consequently in a delayed diagnosis. Reintervention was eventually performed 6 days after negative CT scanning due to deteriorating clinical course and this group had the worst clinical outcome with a mortality rate of 63%. Sometimes the nature of developing anastomotic leaks, with initially mild and only later more pronounced clinical features, contributes to a delay in diagnosis. The reason for CT scanning in the first place was the presence of clinical symptoms, including abdominal pain and an increased C-reactive protein. Other diagnoses, e.g. pneumonia or urine tract infection, were excluded by absence of positive sputum, urine or blood cultures or infiltrates on chest X-ray and abnormalities on CT scanning. All eight patients with delayed diagnosis of anastomotic leakage further deteriorated after the first CT scan, but at which point the earlier negative CT scan is abandoned as decisive is extremely difficult to say and differs per patient.

Mortality rate in patients who underwent immediate reintervention was also high (36%). In these patients initial subtle clinical signs had caused delay in performing a CT scan. By the time a (false) negative CT scan was obtained, clinical signs prompted reintervention. The deterioration of these patients by the time of CT scanning is illustrated by the high mortality rate compared with the patients who underwent immediate reintervention after positive CT scanning. There was no influence of the clinical status of elective versus emergency patients. It is likely to suggest that patients who undergo emergency surgery are deteriorated more at time of surgery than patients who are electively planned for surgery and this consequently might influence the postoperative course. Although numbers were small, in our study outcome after a negative CT scan was not worse for emergency surgery patients compared with elective surgery.

In addition, when re-evaluating the CT features of these 8 patients in group 3b with delayed treatment, the CT features were not different from the scans of the remaining patients with a negative CT outcome. Although we found slight abnormalities, such as limited free fluid or air, these findings were interpreted as 'compatible with recent surgery', as were seen in the other patients. It has been described before that, especially in the early postoperative period, intra-abdominal fluid or extra-luminal air may very well be a normal consequence of recent abdominal surgery and postoperative CT features between patients with and without leakage are sometimes comparable.[7,27,31-33] Furthermore, rectal contrast was not

routinely given in patients with more proximal anastomoses. We excluded patients who underwent rectal resections to increase homogeneity. It is discussed in the literature that contrast may not always leak through the disrupted anastomosis or not even reach a more proximal anastomosis.[25,26,32]

This study demonstrates the importance of clinical status in addition to radiological outcome. The value of clinical parameters has been discussed previously.[18,19,30,31] Recently, Gervaz et al created a risk score including a combination of laboratory and radiology parameters.[34] It becomes more and more clear that neither clinical condition nor radiological outcome should be assessed independently from each other. We are in need of prospectively generated evidence based scoring systems using clinical parameters and radiologic imaging, together, in order to come to a timely diagnosis of anastomotic dehiscence.

A limitation of this study is its retrospective character, although this is in concordance with current clinical practice. The indication for CT scanning, intervention or 'wait and see' is subject to a doctor's personal opinion or experience. Considerations in decision making had been well documented and were very clear from our clinical records, but with comparable clinical and radiological results decision making differs among surgeons. In our hospital, standardized postoperative scoring systems, protocols and twice daily clinical examination of patients by residents, supervised by experienced gastro-intestinal surgeons is part of standard care. Furthermore, CT scans are reviewed by experienced radiologists or by residents, always supervised by a radiologist. CT scans were scored using standardized protocols. In the literature different definitions of clinical and radiological anastomotic leakage are used.[27,35] Nicksa et al demonstrated that sensitivity increased from 0.15 to 0.48 when other criteria were used to define radiological leakage.[26] This supports the need for uniform radiological and clinical criteria to define and quantify the probability of anastomotic leakage.

CONCLUSION

In conclusion, both clinical parameters and radiologic imaging are important in the diagnosis of anastomotic leakage after colonic surgery. A negative CT scan should not reassure us: it should be regarded as a 'snapshot' and any clinical deterioration should prompt us to reconsider the diagnosis and, if necessary, to perform a relaparotomy.

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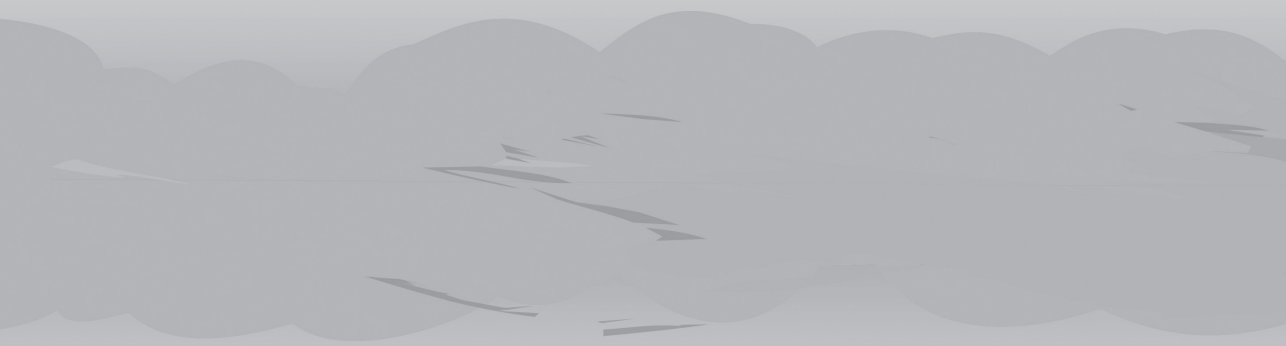

Chapter 8

Early COmplication Detection after colORectal surgery (CONDOR): study protocol for a prospective clinical diagnostic study

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ABSTRACT

Purpose

Anastomotic leakage is one of the most feared complications following colorectal surgery with a high morbidity and mortality rate. Multiple risk factors have been identified, but leakage still occurs. Early detection is crucial in order to reduce morbidity and mortality. The aim of this study is to create a decision algorithm for early detection of anastomotic leakage.

Methods

All patients who undergo elective colorectal surgery for benign or malignant disease are enrolled in this multicenter study. The primary endpoint is the accuracy of the prediction of anastomotic leakage. The main study parameter is the occurrence of postoperative anastomotic leakage. Secondary study parameters are: clinical (vital) parameters, additional laboratory or radiology examination, other complications, mortality, reintervention, duration of hospital and intensive care stay, emergency room visits, readmission to the hospital, and total costs. Daily physical examination and each step in clinical decision making will be evaluated prospectively in a standardized manner. The focus of the analysis will be on the added value of diagnostic tools, such as laboratory results and imaging studies, over physical examination by using logistic regression and decision tree analysis.

Conclusion

This study aims to develop an optimal diagnostic algorithm that can act as a guideline for surgeons or surgical residents to early identify patients with anastomotic leakage after colorectal surgery.

BACKGROUND

Anastomotic leakage is the most feared complication after colorectal surgery and can be life threatening if not rapidly diagnosed and treated. Over the past decades many measures have been taken to decrease leakage rates. Present day, leakage rates have stabilized, but remain as high as 1-19%, with substantial mortality rates up to 39%.[1]

Early detection of these patients is of utmost importance, but diagnosing anastomotic leakage may be a major challenge. In outspoken cases, the decision to reoperate can easily be made without additional radiological imaging modalities, but when symptoms are subtler, prompt diagnosis is difficult. Several clinical parameters have been shown to be associated with anastomotic leakage[2], but when symptoms are more subtle, the time interval between the onset of symptoms and final diagnosis is often delayed, especially if a weekend is included within the time interval.[3] In a previous study we demonstrated that the mortality rate after missed or delayed diagnosis was as high as 62.5%. In contrast, mortality after early detection was less than 10%.[4]

Radiological imaging may contribute to clinical decision making and abdominal computed tomography (CT) scanning is generally the most preferred imaging tool. The literature on the value of abdominal CT scanning is limited and of poor quality as criteria are ill-defined and different CT features may also be interpreted differently, leading to inconclusive CT outcomes and secondary delay in diagnosis or unnecessary reoperations in patients without anastomotic leaks.[4-5]

The CONDOR-study is a multicenter prospective trial that aims to develop an optimal clinical diagnostic strategy to early identify postoperative anastomotic leakage. The accurate evaluation of each step during the postoperative course in this study and insight in the added value of different clinical parameters, will lead to better understanding and clinical decision making. An optimal diagnostic strategy will improve the quality and safety of care and effectiveness of the management of critically ill patients.

METHODS

Study objectives

This study aims to develop an optimal clinical diagnostic algorithm to detect patients with anastomotic leakage after colorectal surgery. The algorithm is based on postoperative physical examination, the added value of laboratory examination and, subsequent radiological imaging.

Study design

The CONDOR study is a prospective clinical diagnostic study, in which postoperative clinical decision making will be evaluated. The value of individual tools (i.e. physical examination, vital parameters, laboratory examination, radiological studies and diagnostic surgical intervention), and the added value of each individual tool, will be assessed. Together with a decision tree analysis, this study will provide an optimal diagnostic decision algorithm in postoperative management of patients who undergo colorectal surgery. This algorithm aims to lead to earlier detection of anastomotic leakage.

Setting

Multicenter study in four large teaching hospitals and one university hospital.

Study population

All patients ≥ 18 years undergoing elective colorectal surgery with a primary intestinal anastomosis (ileo-colic, colonic or colorectal), with or without deviating stoma, will be eligible for inclusion in the study. Exclusion criteria are: age < 18 years, emergency surgery for colonic perforation, proven infection at time of inclusion / surgery, diverticulitis or colitis and patients in whom only a small intestinal anastomosis is performed.

Endpoints and study parameters

Primary endpoint is the accuracy of the diagnosis of postoperative anastomotic leakage.

Primary study parameter:

- The occurrence of anastomotic leakage.

Secondary study parameters:

- All clinical (vital) parameters (which will be described in detail in the next paragraph).
- Additional laboratory examination.
- Additional radiology imaging.
- All individual postoperative complications (in-hospital).
- Mortality (in-hospital or within 30 days postoperatively).
- Reoperations or re-interventions.
- Duration of hospital and intensive care stay.
- Readmission to the hospital within 30 days after discharge.
- Emergency room visits.

The parameters are summarized in table 1.

Table 1. Definition of the different primary and secondary endpoints

Endpoint	Definition
Anastomotic leakage	Anastomotic dehiscence visualized at relaparotomy or endoscopy or percutaneous or transanal drainage of pus from next to the anastomosis or of enteral contents.
Morbidity	All individual complications, as descibed below.
Intestinal ischemia	Ischemia of the small or large intestines, visualized at abdominal CT-scan or colonoscopy requiring intervention.
Intestinal perforation	Free intra-abdominal air on Abdominal X-ray or CT-scan, visualized at relaparotomy.
Enterocutaneous fistula	Abnormal connection between the gastro-intestinal system and the skin with loss of faecal content.
Fascia dehiscence	Clinical dehiscence of the fascia, requiring intervention.
Sepsis	Systemic inflammatory response syndrome (SIRS) in combination with (local) infection with or without organ failure. SIRS: including two or more of the following criteria: - Temperature > 38 degrees or < 36 degrees. - Heart rate > 90 beats per minute. - Respiratory rate > 20 per minute. - Leukocyte count: > 12 x 10^9 per liter or < 4.0 x 10^9 per liter
Intra-abdominal abscess	Fever with or without an increased C-reactive protein and/or lekocyte count in combination with an abnormal collection of pus or infected material on ultrasound or CT-scan.
Ileus	Nausea, vomiting and the absence of stool.
Wound infection	Surgical site infection with purulent discharge from the wound or drain, organisms isolated from aseptically obtained wound cultures and including at least one of the following: redness, heat, pain, tenderness, localized swelling.
Bleeding	Decrease in serum haemoglobin level requiring transfusion and/or re-intervention.
Cardiac	Cardiac arrhythmias requiring medication or intervention; cardiac failure visualized on chest X-ray; myocardial infarction on electrocardiogram or ultrasound with or without increased troponin levels.
Respiratory	Pneumonia, visualized on X-ray and/or positive outcome of a sputum culture requiring antibiotic treatment, respiratory insufficiency requiring intubation and ventilation.
Thrombo-embolic	Radiological proven deep venous thrombosis or pulmonary embolism.
Cerebrovascular	Complication in which an area of the brain is temporarily or permanently affected by bleeding or lack of blood flow, proven on cerebral CT scan.
Urinary tract infection	Clinical symptoms in combination with positive urine sediment or urine culture requiring antibiotic treatment.
Delirium	Neuropsychiatric complication with acute confusional state, requiring medication.
Mortality	Death during hospital stay or within 30 days postoperatively.
Re-intervention	Relaparoscopy, (re)laparotomy, radiological intervention (i.e. drainage).
Stay on intensive care	Stay on the intensive care unit postoperatively.
Hospital stay	Total length of hospital stay starting from the first postoperative day until discharge.
Readmission	Readmission to the hospital within 30 days after discharge.
Emergency room visit	Visit to the emergency room for medical related symptoms.

Ethics and informed consent

The CONDOR study is conducted in accordance with the declaration of Helsinki. The study protocol was approved by the United committees involving human research ("Wet Medisch Wetenschappelijk Onderzoek met Mensen"), the medical ethical committee of the trial coordinating centre. The local institutional review board waived the need for informed consent. Participation in the study does not oppose a risk greater or different from the general surgical treatment of patients with an indication for colorectal surgery. There is no burden of participation. Possibly patients will benefit from participation since regular and standard physical examinations will be done.

Diagnostic tests

Full examination will consist of:

1. Pre-operative clinical characteristics and intra-operative parameters (table 2). Parameters will be scored on case record forms (CRF).

2. Postoperative examination (table 2):

- Daily clinical examination at a set time point and monitoring of vital parameters
- Laboratory examination (if deemed necessary)
- Radiological imaging (if deemed necessary).

From the first postoperative day until discharge or reaching the event (anastomotic leakage), the patients will undergo a standardized clinical assessment once a day, in the morning (figure 1). The treating surgeon or surgical resident ('doctor') will each time be asked to indicate whether or not the patient is suspected to suffer from anastomotic leakage on a VAS (visual analogue scale) score of 0 to 10. Then, the doctor is asked whether he/she needs laboratory measures. If so, again he/she will score the probability of leakage after having looked at the results of this laboratory test. Afterwards, the same question accounts for the need for radiological imaging. If answered yes, and after having gotten the results of imaging, again the doctor is asked to grade the suspicion of anastomotic leakage. Finally the doctor indicates whether or not an intervention will be needed. Each step will be recorded on CRFs. Physical examination and clinical decision making will be performed by both residents and surgeons, since this will reflect the daily practice in participating hospitals. In all participating hospitals, major decisions such as performing a relaparotomy will always be a surgeon's decision. The patient reaches the end of these standard examinations when an anastomotic leakage is detected or when the patient is discharged from the hospital. The gold standard in the diagnosis of anastomotic leakage is the presence of a dehiscent anastomosis at relaparotomy/-scopy or the efflux of feces from a percutaneous drain.

Clinical parameters

All parameters (which were based on the daily practice and literature) will be scored on CRFs[1-2]: clinical condition, mental condition, absence of stool, vital parameters: respiratory

Table 2. Pre-/intra- and postoperative parameters

Preoperative parameters
- Age
- Sex
- Length, weight, BMI
- ASA score
- Smoking
- Use of alcohol
- Use of medication: steroids / anticoagulants / antihypertensive drugs
- Comorbidity: cardiovascular, thrombotic, diabetes mellitus, respiratory, gastro-intestinal, neurological, urogenital, muscles, endocrine system, infection, malignant disease, other.
- Neoadjuvant therapy
- History of abdominal surgery
Intra-operative parameters
- Surgery
- Surgeon and experience
- Additional procedures
- Approach: open or laparoscopic procedure
- Type of anastomosis
- Technique of anastomosis
- Distance of anastomosis to anal verge
- Performance of an entero-stomy
- Duration of surgery
- Intraoperative blood loss
- Intra-operative blood transfusion
Postoperative clinical examination
- Clinical condition
- Mental condition
- Abdominal distension
- Signs of an ileus
- Nasogastric tube
- Absence of stool
- Drainage
- Vital parameters: respiratory rate, heart rate, blood pressure, temperature, urine production

rate, heart rate, blood pressure, temperature, urine production. These parameters include all variables of the well known Early Warning Score (EWS).[6]

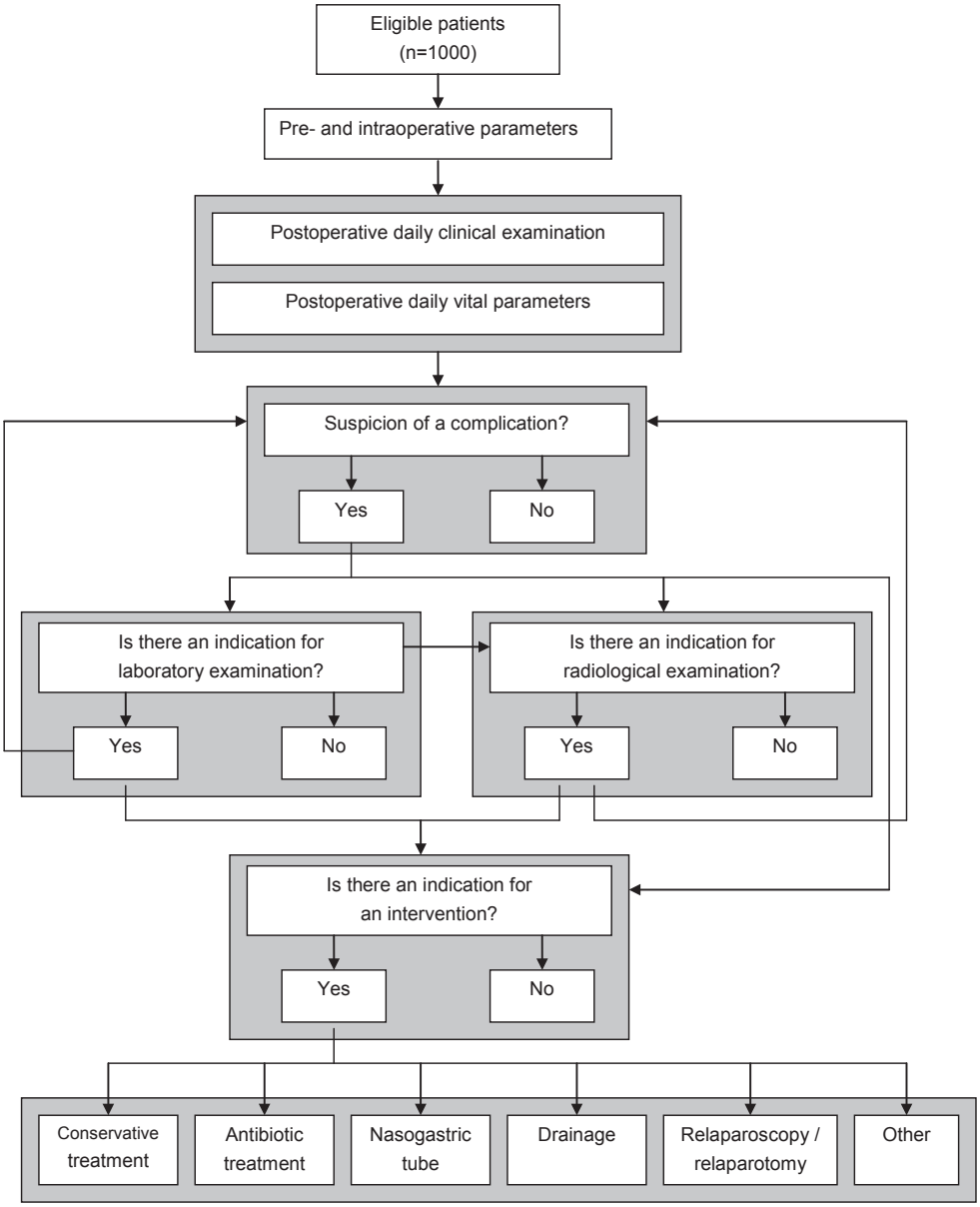

Figure 1. Flow chart of the study protocol

A *laboratory examination* includes: haemoglobin level, C-reactive protein, leukocyte count, serum creatinine, urea, electrolytes (potassium, sodium). This examination will be performed according to local protocol and if deemed indicated. Laboratory results are interpreted after collecting and scoring previous mentioned parameters.

Additional *radiological imaging tools* will only be performed when indicated. This decision will be made by the treating surgeon or surgical resident. If an abdominal CT scan is considered, standardized radiological CT-parameters will be scored on CRFs.

Outcome measures

Follow-up

Duration of follow-up will be two weeks after discharge or the first outpatient visit. This includes all available information regarding pathology results, "out-of-hospital" complications or mortality and emergency room visits.

Table 3. Incidences of anastomotic leakage

Reference	Incidence of leakage
Literature[1].	1-19%
Dutch surgical colorectal audit[7]: - Colonic resections - Rectal resections	Mean 8.4% 8.0% (2010), 6.5% (2011), 6.5% (2012) 12% (2010), 9.2% (2011), 8.0% (2012)
Retrospective cohort study St.Antoniushospital, Nieuwegein, the Netherlands (malignant colorectal surgery between 2009-2011, n=389)	14.9%

Statistical considerations

Sample size

This study is powered to come to an early diagnosis of anastomotic leakage. A mean incidence of anastomotic leakage after colorectal surgery of 10% was used, which was calculated by combining incidences from the literature[1], the Dutch Surgical Colorectal Audit (DSCA)[7] and our own retrospective data from the St. Antonius hospital, Nieuwegein, the Netherlands (table 3). To be able to evaluate at least 100 patients with anastomotic leakage a total of 1.000 patients who undergo colorectal surgery with primary anastomosis is needed. This sample size will also provide sufficient data to evaluate other postoperative complications.

Statistics

Final analysis will be done after follow up of the final patient is completed and sufficient patients with anastomotic leakage have been included. Main endpoint and the occurrence of study parameters will be evaluated according to the definitions listed in this protocol (table 1). Continuous data will be expressed as mean with standard deviation (SD) for normally distributed data or median with inter quartile range (IQR) for not normally distributed data. Dichotomous data and counts will be expressed in frequencies and numbers. Normal distribution will be assessed by visually inspecting the histograms and the Kolmogorov-Smirnov test. Missing data will be explored and, if the percentage exceeds 10% multiple imputations will be performed.

Analyses

1. In general:

A baseline table will be created for all patient in the study. Differences between groups, i.e. patients with anastomotic leakage versus no leakage, will be tested using the Mann-Whitney-U test for data that is not normally distributed, the independent two sample t-test for data with a normal distribution, or the Chi-square test for binomial data. All probability values are two-tailed. $P < 0.05$ will be used as level of significance.

2. Development of a diagnostic algorithm:

First, independent risk factors for the occurrence of anastomotic leakage will be identified using a multiple logistic regression model.

Second, sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV), likelihood ratios and accuracy will be calculated for each individual diagnostic step, including physical examination, laboratory examination, radiological imaging, and for a combination of parameters as a stepped approach (i.e. physical examination and laboratory results, etcetera).

Finally, decision tree analysis will be used to determine risk groups and to develop an optimal diagnostic strategy for the identification of patients at risk for postoperative anastomotic leakage.

Study period

In a large teaching hospital yearly at least 150 patients will be eligible for inclusion in this study. Given the number of 1.000 patients needed for this study, the expected drop out of 10% of patients, after participation of four other hospitals, the expected inclusion will be completed within two years.

DISCUSSION

Early detection of anastomotic leakage after colorectal surgery is crucial but often challenging. Delay in diagnosis leads to increased morbidity and mortality. Surgeons and residents will be triggered to allow early identification of patients with deteriorating clinical conditions. The accurate evaluation of each step during the postoperative course will lead to better understanding and clinical decision making. An optimal diagnostic strategy will improve the quality and safety of care and effectiveness of the management of patients suspected for anastomotic leakage.

In conclusion, the CONDOR study is a multicenter study which aims to develop an optimal diagnostic strategy regarding the value of additional imaging tools (i.e. computed tomography scans) over pre-and peri-operative risk-assessment, postoperative physical examination and laboratory examination, to detect postoperative complications after colorectal surgery for colorectal disease.

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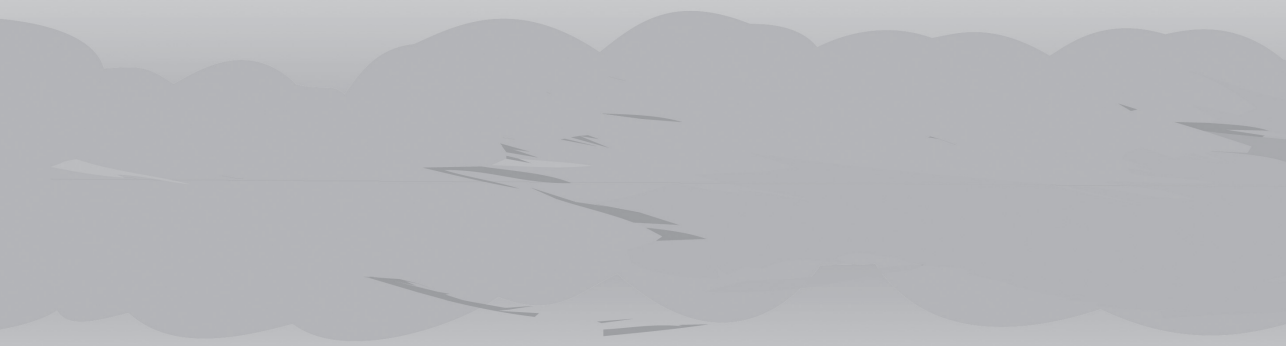
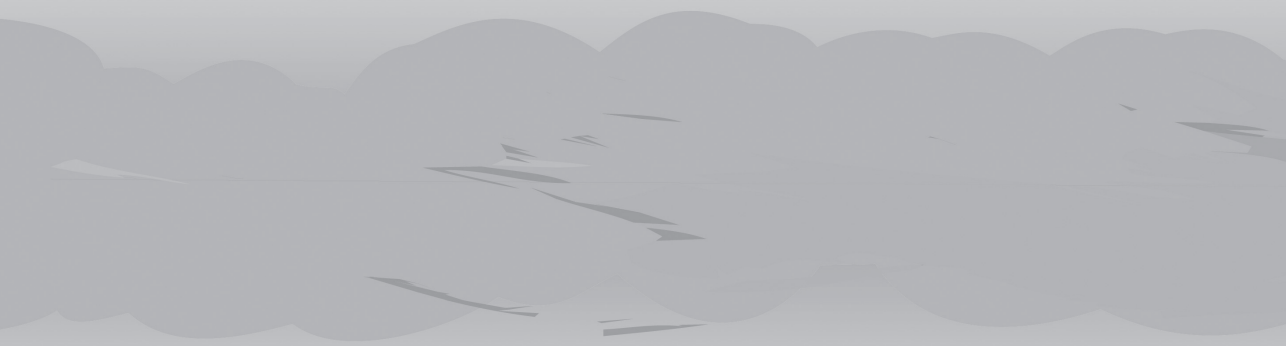


PART VI

Functional outcome and quality of life after colorectal surgery



Chapter 9

Predictors of impaired functional outcome and related quality of life after TME with primary anastomosis for rectal cancer

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Annals of Coloproctology 2015;31(1):23-28

ABSTRACT

Background

After total mesorectal excision (TME) with primary anastomosis for patients with rectal cancer, the quality of life (QoL) may be decreased due to fecal incontinence. This study aimed to identify predictors of fecal incontinence and related QoL.

Methods

Patients who underwent TME with primary anastomosis for rectal cancer between December 2008 and June 2012 completed the fecal incontinence quality of life scale (FIQoL) and Wexner incontinence score. Factors associated with these scores were identified using a linear regression analysis.

Results

A total of 80 patients were included. Multivariate analysis identified a diverting ileostomy (n = 58) as an independent predictor of an unfavorable outcome on the FIQoL subscale coping/behavior (P = 0.041). Ileostomy closure within and after 3 months resulted in median Wexner scores of 5.0 (interquartile range [IQR], 2.5–8.0) and 10.5 (IQR, 6.0–13.8), respectively (P < 0.001). The median FIQoL score was 15.0 (IQR, 13.1–16.0) for stoma closure within 3 months versus 12.0 (IQR, 10.5–13.9) for closure after 3 months (P = 0.001).

Conclusion

A diverting ileostomy is a predictor for an impaired FIQoL after a TME for rectal cancer. Stoma reversal within 3 months showed better outcomes than reversal after 3 months. Patients with a diverting ileostomy should be informed about the impaired QoL, even after stoma closure.

INTRODUCTION

A total mesorectal excision (TME) is the surgery of choice for patients with rectal cancer. Preferably a sphincter-saving procedure is advocated.[1] Oncological results are comparable to those for the formerly-preferred abdominoperineal resection (APR).[2] The reason for sphincter preservation is the supposed better quality of life (QoL) compared with the QoL for patients with a permanent stoma after APR. Although sphincter preserving surgery has become the surgery of choice for treating patients with rectal cancer, a recent review demonstrated that up to 90% of the patients developed changes in bowel habit, including fecal incontinence.[3] This may negatively influence the QoL. A meta-analysis demonstrated comparable general QoL for both the low anterior resection and the APR[4], but individual domains of QoL scores showed inconclusive results.[4,5] Different causal mechanisms of the decreased bowel function after sphincter-saving surgery have been investigated. The definitive cause still remains unresolved and seems to be multifactorial.[3] This study aims to identify predicting factors for fecal incontinence and related QoL after sphincter-saving surgery for the treatment of rectal cancer.

MATERIAL AND METHODS

Patients that had TME surgery for rectal cancer from December 2008 until June 2012 by using sphincter preservation with a primary anastomosis were included. Patients were treated in two hospitals: a teaching hospital (St. Antonius Hospital, Nieuwegein, The Netherlands) and a district hospital (Rivierenland Hospital, Tiel, The Netherlands). The patients' characteristics were retrospectively collected from their charts. A rectal tumor was defined as a tumor below an imaginary line from the upper part of the pubic symphysis and the promontory on sagittal reconstructions of the pelvic magnetic resonance imaging (MRI) scan. In the case of sigmoidoscopy, the definition of a tumor less than 15 cm from the anal verge was used. Comorbidity was scored using the age-adjusted Charlson comorbidity index (CCI) and the International Classification of Diseases, 10th revision, for diagnosis coding.[6,7] Patients were subdivided into low (≤5 cm), mid (>5 cm, ≤10 cm) or high (>10 cm, ≤15 cm) rectal tumor groups based upon MRI. The sigmoidoscopy report was used when the distance of the tumor to the anal verge was missing from the MRI report. Preoperative therapy was either short-course radiotherapy (5 × 5 Gray) or a combination of long-course radiotherapy (25 × 2 Gray) with chemotherapy. One center treated all patients with perioperative pelvic floor muscle training (PFMT), which consisted of at least four consultations with a specialized physiotherapist.

Complications were measured during the first 30 days following surgery. An anastomotic leakage was defined as the presence of leakage or a presacral abscess on an abdominal computed tomography-scan with oral, rectal, and intravenous contrast. A stoma-related complication included a high output stoma, a prolapse of the small bowel, necrosis, or a nonproducing stoma because of stenosis. The surgery was executed according to the TME technique by using laparoscopy or laparotomy. High ligation of the mesenteric inferior vessels and mobilization of the splenic flexure were performed. Dissection of the rectum was carried to the pelvic floor with nerve preservation. Reconstruction was a side-to-end stapled colorectal anastomosis. Possible predictors that were tested were age, gender, body mass index, CCI, distance of the tumor to the anal verge, perioperative PFMT, pre-operative treatment, a diverting (ileo)stomy, blood loss, duration of surgery, anastomotic leakage, stoma-related complications, reoperation, tumor stage, and time interval to completion of the questionnaire.

Fecal incontinence and the QoL outcomes were measured using the validated fecal incontinence quality of life scale (FIQoL) and the Wexner incontinence score, both adapted to the Dutch language.[8,9] FIQoL includes four different subscales: lifestyle, coping/behavior, depression/self-perception and embarrassment. The total FIQoL score is the sum of all four subscales. Subscale scores range from 1 to 5 and are the average response to all items on the scale. A lower score indicates a lower functional status and related quality of life.[8] A higher Wexner score indicates more symptoms of fecal incontinence on a scale from 0 to 20.[9]

One researcher (M.S.W.) contacted eligible patients to ask then to voluntarily participate in the study. Self-administered questionnaires were sent to patients by e-mail or letter. Phone-call reminders were made to nonresponders. Patients with a diverting stoma in situ at the time of answering the questionnaire were excluded from the analysis. The time interval to completing of the questionnaire was measured from the day of restored bowel continuity until the day of answering the questionnaire.

Statistical analysis

The data were analyzed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). A statistician was asked for advice concerning the analysis. The values of the patients' characteristics are given as a median and IQR for all continuous data. Values of binomial data are shown as a number of patients and percent of group. The relationship between possible predictors and outcome was analyzed using a univariate linear regression analysis. Variables associated with our outcomes ($P < 0.100$) were entered into a multivariate linear regression analysis. Differences between groups were tested using the independent

two-sample t-test within normally distributed data and the Mann-Whitney U-test within non-normally distributed data. Normality was tested by using the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical variables between groups. A value of $P < 0.05$ was used as the level of significance.

RESULTS

During this study period, TME was performed on 138 patients at the two participating hospitals. A total of 99 patients were contacted. The remaining 39 patients were excluded from this study due to death during follow-up (n = 14), a stoma in situ (n = 19), creation of an end colostomy (n = 2), or loss to follow-up (n = 4). Finally, 80.8% (n = 80) of the contacted patients responded and were included.

The patients' characteristics are summarized in Table 1. The median age of the included patients at the time of surgery was 63 years (IQR, 57–69 years), and 66.3% (n = 53) were male. Patients predominantly had midrectal tumors (n = 42, 52.5%) with a median distance of the tumor from the anal verge of 9.0 cm (IQR, 6.0–12.0 cm). The median time interval to completion of the questionnaire was 19 months (IQR, 10–29 months). Five patients (6.3%) had an anastomotic leak as a complication. Four of them received a diverting ileostomy at the primary surgery, and the other received a diverting ileostomy after having been diagnosed with this complication.

The median Wexner score was 7.0 (IQR, 4.0–12.0) (Table 2). Five predicting factors for a higher Wexner score (unfavorable outcome) were identified in the univariate analysis: perioperative PFMT, preoperative therapy, a diverting ileostomy, longer duration of surgery, and a stoma-related complication. In the multivariate regression analysis, none of these factors was independently associated with a higher Wexner score (data not shown).

The median FIQoL scores are depicted in Table 2. In the univariate analysis, four variables had a relationship with the FIQoL subscale coping/behavior: preoperative therapy, a diverting ileostomy, an anastomotic leak, and a stoma-related complication. Multivariate regression analysis revealed a diverting ileostomy (B= –0.524; 95% CI, –1.072 to –0.021; P = 0.041) as an independent predictor of an unfavorable outcome (Table 3). In the univariate analysis, a variety of predictors were identified for an unfavorable outcome of other FIQoL subscale scores. Multivariate analysis of perception, or FIQoL total score did not show independently associated factors with our outcome.

Table 1. Patient characteristics

	All patients (n = 80)
General characteristics	
Age (years)	63 (57-69)
Male/female (n)	53 (66.3%) / 27 (33.8%)
BMI (kg/m^2)	26.3 (23.8-28.7)
CCI	4 (4-6)
TNM stage (UICC)	
- I (n)	26 (32.5%)
- II (n)	18 (22.5%)
- III (n)	33 (41.3%)
- IV (n)	3 (3.8%)
Distance of the tumour from the anal verge (cm)	9.0 (6.0-12.0)
- ≤ 5 cm (n)	9 (11.3%)
- 6-10 cm (n)	42 (52.5%)
- 11-15 cm (n)	29 (36.3%)
Perioperative PFMT (n)	32 (40.0%)
Preoperative therapy (n)	62 (77.5%)
- Short-course radiotherapy	46 (57.5%)
- Long-course radiochemotherapy	16 (20.0%)
Operative characteristics	
Approach (n)	
- Laparoscopy	66 (82.5%)
- Lapatoromy	11 (13.8%)
- Conversion	3 (3.8%)
Additional procedures (n)	
- Diverting ileostomy / colostomy	58 (72.5%) / 3 (3.8%)
Blood loss (mL)[a]	100 (30-350)
Duration of surgery (min)	163 (123-240)
Postoperative characteristics	
Length of hospital stay (days)	6 (5-10)
Complications (n)	
- Anastomotic leak	5 (6.3%)
- Stoma-related complication	9 (11.3%)
- Re-operation	7 (8.8%)
Time interval of completing questionnaire (months)	19 (10-29)

Values are given as number of patients (n) and percent (%) of group or median (IQR). BMI, Body mass index; CCI, Charlson comorbidity index; UICC, Union for International Cancer Control; PFMT, pelvic floor muscle training; min, minutes. [a] Data adds up to 75 because of occasional missing data.

Table 2. Wexner and FIQoL scores

	All patients (n = 80)
Wexner score	7.0 (4.0-12.0)
FIQoL score	
- FIQoL total	13.4 (11.4-15.7)
- FIQoL lifestyle	3.5 (3.0-4.0)
- FIQoL coping/behaviour	2.9 (2.4-3.7)
- FIQoL depression / self-perception	3.9 (3.3-4.3)
- FIQoL embarrassment	3.5 (3.0-4.0)

Values are given as median (inter quartile range). FIQoL, Fecal Incontinence Quality of Life Scale.

Table 3. Multivariate linear regression analysis: FIQoL

	B (95% CI)	**p-value**
FIQoL coping/behavior		
- Preoperative therapy (yes)	-0.043 (-0.572-0.487)	0.872
- Diverting ileostomy (yes)	-0.524 (-1.072-0.021)	0.041
- Complication: anastomotic leak (yes)	-0.689 (-1.407-0.028)	0.060
- Stoma-related complication (yes)	-0.318 (-0.883-0.248)	0.266

FIQoL, Fecal Incontinence Quality of Life Scale; B, regression coefficient; CI, confidence interval.

Of 80 patients, 58 (72.5%) received a diverting ileostomy at primary surgery and underwent restoration of bowel continuity. The characteristics of these patients are summarized in Table 4. In 17 patients (29.3%), bowel continuity was restored within 3 months following TME, compared with 41 patients (70.7%) in whom bowel continuity was restored 3 months or longer after TME. Only the length of hospital stay differed between these groups. Patients with stoma closure within 3 months had a median length of hospital stay of 6 days (IQR, 5–8 days) compared to 8 days (IQR, 6–19 days) for patients with stoma closure after 3 months (P = 0.009). This was not due to comorbidity or postoperative complications as no differences were found between groups concern-ing these variables (Table 4). Patients in whom bowel continuity was restored within and after 3 months had median Wexner scores of 5.0 (IQR, 2.5–8.0) versus 10.5 (IQR: 6.0–13.8), respectively (P < 0.001). Furthermore, the FIQoL total score was significantly more favorable for patients who had their stoma closed within 3 months compared to those who had their stoma closed after 3 months (median, 15.0; IQR, 13.1–16.0 vs. median, 12.0; IQR, 10.5–13.9, respectively, P = 0.001) (Table 5).

Table 4. Comparing groups: stoma in situ ≤3 months vs. stoma in situ >3 months

	All patients (n=58)	Stoma in situ ≤3 months (n=17)	Stoma in situ >3 months (n=41)	p-value
General characteristics				
Age (years)	63 (54-70)	64 (53-70)	63 (56-70)	0.778
Gender (n)				
- Male	40 (69.0%)	14 (82.4%)	26 (63.4%)	0.268
- Female	18 (31.0%)	3 (17.6%)	15 (36.6%)	0.268
BMI (kg/m^2)	26.0 (23.6-29.1)	26.6 (24.7-29.4)	25.8 (23.2-28.6)	0.488
CCI	4 (3-5)	4 (3-6)	4 (4-6)	0.398
TNM stage (UICC)				
- I (n)	21 (36.2%)	9 (52.9%)	12 (29.3%)	0.159
- II (n)	13 (22.4%)	3 (17.6%)	10 (24.4%)	0.830
- III (n)	24 (41.4%)	5 (29.4%)	19 (46.3%)	0.369
Distance of the tumor from anal verge (cm)	8.0 (5.9-11.3)	9.0 (7.0-11.5)	8.0 (5.5-11.5)	0.321
- ≤ 5 cm (n)	9 (15.5%)	1 (5.9%)	8 (19.5%)	0.365
- 6-10 cm (n)	31 (53.4%)	11 (64.7%)	20 (48.8%)	0.414
- 11-15 cm (n)	18 (31.0%)	5 (29.4%)	13 (31.7%)	1.000
Perioperative PFMT (n)	30 (51.7%)	8 (47.1%)	22 (53.7%)	0.866
Preoperative therapy (n)	54 (93.1%)	17 (100.0%)	37 (90.2%)	0.310
- Short-course radiotherapy	41 (70.7%)	15 (88.2%)	26 (63.4%)	0.116
- Long-course radiochemotherapy	13 (22.4%)	2 (11.8%)	11 (26.8%)	0.365
Operative characteristics				
Approach				
- Laparoscopy (n)	47 (81.0%)	15 (88.2%)	32 (78.0%)	0.594
- Laparotomy (n)	9 (15.5%)	2 (11.8%)	7 (17.1%)	0.912
- Conversion (n)	2 (3.4%)	0 (0.0%)	2 (4.9%)	1.000
Blood loss (mL)[a]	150 (50-400)	100 (35-388)	200 (50-500)	0.241
Duration of surgery (min)	180 (149-258)	155 (120-219)	190 (150-278)	0.087
Postoperative characteristics				
Length of hospital stay (days)	7 (5-14)	6 (5-8)	8 (6-19)	0.009
Complications (n)				
- Anastomotic leak	4 (6.9%)	1 (5.9%)	3 (7.3%)	1.000
- Stoma-related complication	9 (15.5%)	3 (17.6%)	6 (14.6%)	1.000
- Re-operation	6 (10.3%)	2 (11.8%)	4 (9.8%)	1.000
Time interval of completing questionnaire (months)	19 (10-28)	14 (10-24)	19 (12-29)	0.345

Values are given as number of patients (n) and percent (%) of group or median (inter quartile range). *BMI*, Body mass index; *CCI*, Charlson comorbidity index; *UICC*, Union for International Cancer Control; *PFMT*, pelvic floor muscle training; *min*, minutes.

Table 5. Patients with a diverting ileostomy: Wexner and FIQoL scores

	Stoma in situ ≤ 3 months (n=17)	Stoma in situ >3 months (n=41)	p-value
Wexner score	5.0 (2.5-8.0)	10.5 (6.0-13.8)	< 0.001
FIQoL score			
- FIQoL total	15.0 (13.1-16.0)	12.0 (10.5-13.9)	0.001
- FIQoL lifestyle	3.8 (3.4-4.0)	3.0 (2.2- 3.6)	<0.001
- FIQoL coping/behaviour	3.2 (2.7-3.6)	2.5 (2.1-3.0)	0.011
- FIQoL depression / self-perception	4.1 (3.8-4.4)	3.4 (2.8-4.1)	0.001
- FIQoL embarrassment	3.7 (3.3-4.0)	3.3 (2.7-3.7)	0.018

Values are given as median (inter quartile range). FIQoL, Fecal Incontinence Quality of Life Scale.

DISCUSSION

In this study, a temporary ileostomy independently predicted impaired FIQoL concering coping and behavior, after stoma closure, in patients treated with a TME for rectal cancer. This means that patients stay near a restroom, worry about being at a toilet in time, feel like they have no control over their bowels, and have less sex than they would like to have. In addition, patients with stoma reversal within 3 months showed better functional outcome and related QoL. All other variables associated with the Wexner and the FIQoL scores in the univariate analysis were shown not to be independent predictors in the multivariate analysis. To our knowledge, the negative value of a temporary ileostomy on the FIQoL after stoma closure has never been described. Four studies investigated a diverting ileostomy as a possible predictor for impaired functional outcome, but none of the results reached significance.[10-13] Several studies showed an impaired functional outcome after TME in patients who had a low anastomosis and patients who had preoperative radiotherapy, but our study did not reveal these items as risk factors.[11-16] Anastomotic leakage negatively affected FIQoL or bowel function in one study[12], but this association was not found in several other studies.[10,11,13,14,17,18] Lange et al[11] identified height of tumor and excessive blood loss as predictors of fecal incontinence, but only in patients who received preoperative radiotherapy. Furthermore, age[13], gender[14], and operative blood loss[13] had a relationship with bowel function following TME in other studies.

The presence of a temporary ileostomy significantly reduces the QoL of patients.[19,20] Also, with a temporary stoma, there is the need for a second operation, which has additional morbidity.[21] Furthermore, our study shows that a temporary ileostomy impairs FIQoL even after stoma closure. Risks of developing an anastomotic leakage and of having to undergo related reoperations increase if a stoma is omitted at primary surgery.[22,23] Therefore, we

cannot advocate the omission of a temporary ileostomy. Still, patients should be informed about the impact of an ileostomy on QoL even after stoma closure, and a permanent colostomy should be considered. When a temporary ileostomy is performed, stoma reversal should be done within 3 months after the TME. The exact reason for a better outcome after early stoma reversal cannot be given. In The Netherlands, stoma reversal after 3 months is not rare. Also, our comparison of patients with different timings of stoma reversal did not show any differences concerning complication rate, comorbidity, tumor height, or tumor stage. Therefore, our outcome does not seem to have been confounded. The long diversion of a colorectal anastomosis is supposed to reduce the functional adaptability of the neorectum. This might be the etiology of more fecal incontinence after stoma reversal.

Our study has some limitations due its retrospective design. Furthermore, patients were recruited from two hospitals with some differences in the protocols. Patients in whom bowel continuity was not restored were excluded for analysis because they were not able to answer questions concerning fecal incontinence. This could have led to selection bias for those patients with anastomotic-related complications. Another limitation is that a preoperative measurement of QoL is missing, and we did not analyze nonresponders. Lastly, the small numbers of anastomotic leakage made our attempt to correct for this parameter in the multivariate analysis difficult. Therefore, this might still be a confounding factor when measuring FIQoL. Baxter et al.[24] states that the perception of the patient must be the foundation of any evaluation of incontinence or the impact of incontinence. Objective measurements for bowel function have been used, but were shown to have low specificity and sensitivity.[24] Therefore, the use of questionnaires is a well-considered decision. The FIQoL and the Wexner incontinence score are the questionnaires that are most suitable for evaluating the QoL and for assessing severity, respectively.[25] The questionnaires were self-administered; consequently, the potential for socially desirable answers was minimized.

CONCLUSION

In conclusion, a diverting ileostomy is a predictor for an impaired FIQoL after a TME for treating rectal cancer. Stoma reversal within 3 months showed a better functional outcome compared with ileostomy closure after 3 months. This might be due to a reduced functional adaptability of the neorectum after diversion. Patients with a temporary ileostomy should be informed preoperatively about the impaired QoL, even after stoma closure.

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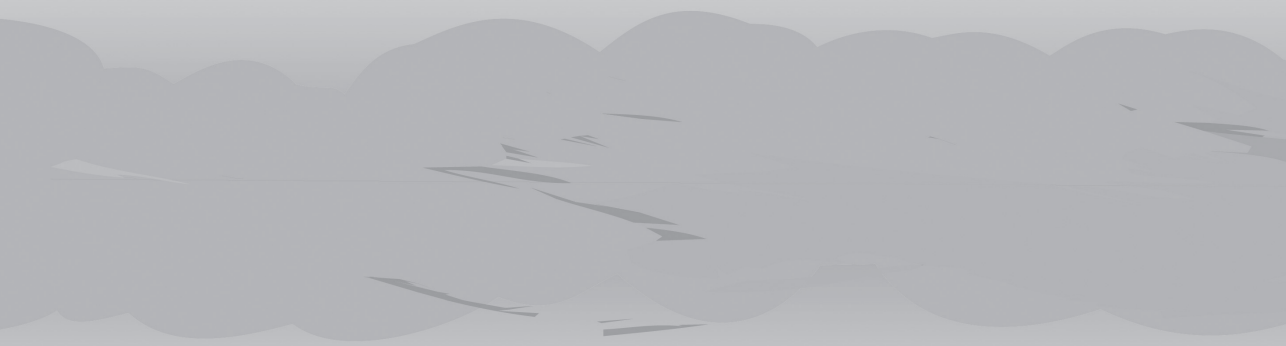

Chapter 10

Quality of life after low anterior resection for rectal cancer in the elderly patient

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ABSTRACT

Purpose

Fecal incontinence is a major concern. Incidence increases with age. Quality of life due to fecal incontinence may be decreased after both sphincter-saving surgery and rectal resection with a permanent stoma. The aim of this study is to investigate the quality of life, with regard to fecal incontinency, in elderly patients after rectal cancer surgery.

Methods

All consecutive patients who underwent elective rectal surgery with anastomosis for rectal cancer between December 2008 and June 2012 at two Dutch hospitals were found to be eligible for inclusion. Wexner and FIQoL scores were collected. Younger and elderly (≥ 70 years) patients were compared.

Results

A total of 79 patients were included. There were 19 elderly patients (24.1%). All diverting stoma's that had been placed (n=60; 75.9%), had also been closed at time of the study. There were no differences in Wexner or FIQoL scores between younger patients and elderly. Also, there were no differences between patients without a diverting stoma or patients in whom bowel continuity was restored. Elderly females had significantly worse scores on the FIQoL subscales coping/behavior (p=0.043) and depression/self-perception (p=0.004) compared with younger females. Elderly females scored worse on coping/behavior (p=0.010) and depression/self-perception (p=0.036) compared with elderly males. Younger and elderly males had comparable scores.

Conclusion

Quality of life with regard to fecal incontinency is worse in elderly females after sphincter-preserving surgery for rectal cancer. Patients should be informed about this impact and a definite stoma may be considered in this patient group.

INTRODUCTION

With age, function of the anal sphincter and anorectum changes.[1] Fecal incontinence is a major concern, especially in the elderly and may affect up to 65% of nursing home residents.[2] Also, with aging of the population, the incidence of cancer increases and more elderly will undergo surgery for rectal cancer.[3-5] Although oncological results are equal, rectal surgery with sphincter preservation may be preferred above abdominal perineal resections in which a permanent stoma is created, since a stoma is supposed to seriously limit quality of life.[6] Nonetheless, literature on a better quality of life after either sphincter-saving surgery or abdominal perineal resection is controversial and a wide spectrum of symptoms due to changes in bowel habit, including fecal incontinence and anorectal dysfunction have been described.[7-10] Although overall quality of life of elderly seemed similar to that of younger patients in a recent review[11], fecal incontinence is a major concern in elderly patients, even without surgery. This raises the question whether sphincter-functions should be preserved in the elderly or to choose rectal resection with the creation of a permanent stoma. To gain more insights in this topic, we investigated the quality of life, in terms of fecal incontinency, in elderly patients following rectal cancer surgery and compared these results with a younger group of patients.

METHODS

All consecutive patients who underwent elective rectal surgery with primary anastomosis for rectal cancer at two Dutch hospitals (St. Antonius Hospital, Nieuwegein, the Netherlands, and Rivierenland Hospital, Tiel, the Netherlands) between December 2008 and June 2012 were found to be eligible for inclusion in this study.

Inclusion criteria were adult patients, rectal carcinoma, rectal resections including anterior and low anterior resection with primary anastomosis. A rectal tumor was defined using sagittal reconstructions of pelvic MRI (a tumor below an imaginary line from the upper part of the pubic symphysis and the promontory) or sigmoidoscopy (tumor less than 15 cm from the anal verge). Exclusion criteria were rectal resections for benign disease, other colorectal resections and procedures without anastomosis, including Hartmann's procedure or abdominoperineal resection.

Surgery was performed according to the total mesorectal excision technique by either laparotomy or laparoscopy. High ligation of the inferior mesenteric vasculature and mobilization of the splenic flexure were performed. The rectum was dissected with nerve

preservation and reconstructed with a side-to-end stapled colorectal anastomosis. In some cases a diverting ileostomy was created.

All data, including demographic data, clinical records, oncological and pathology reports and operative reports were collected into a database. The Charlson Comorbidity Index (age unadjusted) and International Classification of Diseases were used to score comorbidity.[12,13] Follow-up of postoperative morbidity or mortality was at least 30 days postoperatively.

In this study, almost all patients with rectal cancer underwent a full preoperative workup, including a colonoscopy, MRI pelvis or CT pelvis, thoracic and/or abdominal CT scan. All patients were discussed during a multidisciplinary oncology review board. Following the Dutch guidelines for the treatment of colorectal cancer, surgery preceded by irradiation was indicated for all patients with T2-T4 staged tumors. Patients in whom a positive circumferential margin was expected or with the suspicion of four or more tumor positive lymph nodes were preferably treated with chemotherapy (mostly capecitabine 825 mg/m2 bid) during long-term radiotherapy (2 x 25 Gy). For all other patients, a short course of radiation therapy was recommended (5 x 5 Gy).

Outcome measures

The primary outcome was quality of life associated with incontinence, which was measured using the validated Wexner incontinence score and Fecal Incontinence Quality of Life scale (FIQoL).[14,15] All eligible patients were contacted by one researcher to ask for participation in the study and informed consent. After permission, a self-administered questionnaire was sent to these patients by email or by letter. Non-responders were reminded with one extra phone call. All individual aspects of the questionnaires and total scores were collected. The Wexner score ranged from 0 to 20, with a higher score indicating a higher degree of fecal incontinence. The FIQoL scale included four subscales: lifestyle, coping/behavior, depression/self-perception and embarrassment, with each subscale score ranging from 1 to 5. Furthermore, these four subscales were summed resulting in a total FIQoL score. A lower score indicates a worse quality of life due to incontinence. Median time interval between surgery and the questionnaires was 20 months (inter quartile range (IQR) 11-30 months).

Statistical analysis

Patients were divided into a younger and elderly patient group, in which elderly were defined from the age of 70 years and older. Data is expressed as number of patients (with percentage) or median with inter quartile range. The differences between groups were tested using the Mann-Whitney-U test. A p-value inferior to 0.050 was used as level of

significance. The data was analyzed with SPSS statistical software (SPSS Statistics Version 19.0, Inc., Chicago, Illinois, USA).

Table 1. Baseline and peri-operative characteristics

	All patients *(n = 79)*	**Age < 70 years** *(n = 60)*	**Age ≥ 70 years** *(n = 19)*	**p-value**
General parameters				
Age at surgery (years)	63 (57-69)	60 (53-65)	72 (70-78)	< 0.001
Male (n)	53 (67.1%)	39 (65.0%)	14 (73.7%)	0.673
BMI (kg/m^2)	26.4 (23.7-28.8)	26.5 (23.8-28.7)	26.0 (23.5-29.1)	0.991
CCI	2 (2-3)	2 (2-3)	2 (2-3)	0.471
Alcohol	53 (67.1%)	40 (66.7%)	13 (68.4%)	0.887
Smoking	10 (12.7%)	6 (10.0%)	4 (21.1%)	0.386
Previous abdominal surgery	22 (69.9%)	40 (72.7%)	11 (61.1%)	0.525
T-stage (TNM-classification)				
- T1	7 (8.9%)	5 (8.3%)	2 (10.5%)	1.000
- T2	34 (43.0%)	29 (48.3%)	5 (26.3%)	0.155
- T3	36 (45.6%)	26 (43.3%)	10 (52.6%)	0.656
- T4	2 (2.5%)	0 (0%)	2 (10.5%)	0.088
Distance of the tumor from anal verge (cm)	9.0 (6.0-12.0)	8.5 (6.0-12.0)	10.0 (8.0-14.0)	0.089
Neoadjuvant therapy	61 (77.2%)	47 (78.3%)	14 (73.7%)	0.915
- Short-course radiotherapy	46 (58.2%)	33 (55.0%)	13 (68.4%)	0.443
- Chemoradiation	15 (19.0%)	14 (23.3%)	1 (5.3%)	0.157
Intraoperative parameters				
Approach				
- Laparotomy	11 (13.9%)	9 (15.0%)	2 (10.5%)	0.912
- Laparoscopy	65 (82.3%)	49 (81.7%)	16 (84.2%)	1.000
- Conversion	3 (3.8%)	2 (3.3%)	1 (5.3%)	1.000
Diverting stomy				
- Ileostomy	57 (72.2%)	42 (70.0%)	15 (78.9%)	0.642
- Colostomy	3 (3.8%)	3 (5.0%)	0 (0%)	0.760
Duration of surgery (min)	160 (120-240)	160 (120-217)	180 (130-250)	0.704
Blood loss (mL)	100 (30-350)	100 (30-200)	300 (100-500)	0.021
Postoperative parameters				
Length of stay at the hospital (days)	6 (5-10)	6 (4-10)	8 (5-22)	0.022
Complications				
- Anastomotic leakage	5 (6.3%)	5 (8.3%)	0 (0%)	0.448
- Stoma-related complications	9 (11.4%)	7 (11.7%)	2 (10.5%)	1.000
Reoperation / reintervention	7 (8.9%)	5 (8.3%)	2 (10.5%)	1.000

Values are given as number of patients (%) or as median (inter quartile range). CCI: Charlson Comorbidity Index.

RESULTS

Patient and peri-operative characteristics

Rectal resection for rectal cancer was performed in 138 patients during the study period. Fourteen patients died during follow-up, 27 patients had a diverting stoma in situ and another 18 patients were excluded due to unresponsiveness, loss-to-follow up, incomplete data or no permission for inclusion. Finally, 79 of the contacted patients were included. Median age was 63 years (IQR 57-69), with 19 elderly patients (24.1%). There were 53 males (67.1%) and 26 females (32.9%). Median distance of the tumor from the anal verge was 9.0 cm (IQR 6.0-12.0). Upon pathological examination, 8.9% were diagnosed with TNM-stage T1 (n=7), 43.0% T2 (n=34), 45.6% T3 (n=36) and 2.5% T4 (n=2). Neoadjuvant therapy was given in most patients and did not significantly differ between both patient groups. A diverting stoma was placed in 60 patients (75.9%) and at the time of the questionnaire all stomas were closed. Baseline and operation-related characteristics are summarized in table 1. Younger and elderly patients significantly differed with more blood loss and an increased length of stay in elderly patients (table 1).

Wexner and FIQoL scores in elderly

Median Wexner and FIQoL scores are summarized in table 2. There were no significant differences between younger patients and elderly in scores. When analyzing the patients who underwent surgery without the creation of a diverting stomy (n=19), there were no significant differences in Wexner or FIQoL score between younger (n=15) and elderly (n=4) patients. Also, when analyzing patients in whom a bowel continuity was restored after a diverting stoma, there were no significant differences between younger (n=45) and elderly (n=15) patients (data not shown). In elderly patients, there was a trend to a worse FIQoL lifestyle and coping/behavior score, although this was not significant (table 3).

Table 2. Wexner and FIQoL scores

	All patients *(n = 79)*	**Age < 70 years** *(n = 60)*	**Age ≥ 70 years** *(n = 19)*	**p-value**
Wexner score	7.0 (4.0-12.0)	7.0 (4.0-11.8)	7.0 (4.0-14.0)	0.904
FIQoL score				
- Lifestyle	3.5 (3.0-4.0)	3.5 (3.0-4.0)	3.5 (2.3-4.0)	0.831
- Coping / behavior	2.9 (2.4-3.7)	2.8 (2.4-3.7)	3.2 (2.0-3.7)	0.713
- Depression / self-perception	3.9 (3.3-4.3)	3.9 (3.3-4.3)	3.8 (3.2-4.4)	0.908
- Embarrassment	3.5 (3.0-4.0)	3.3 (3.0-4.0)	3.7 (2.9-4.0)	0.876
- Total score	13.4 (11.4-15.7)	13.4 (11.5-15.6)	14.3 (10.7-15.7)	0.804

Values are given as median (inter quartile range).

Table 3. Wexner and FIQoL scores - Age ≥ 70 years

	All patients *(n =19)*	**No stomy** *(n = 4)*	**Restoration of Bowel continuity** *(n = 15)*	**p-value**
Wexner score	7.0 (4.0-14.0)	5.0 (1.0-10.5)	8.0 (4.0-13.0)	0.340
FIQoL score				
- Lifestyle	3.5 (2.3-4.0)	4.0 (3.6-4.0)	3.4 (2.1-3.9)	0.051
- Coping / behavior	3.2 (2.0-3.7)	4.0 (2.5-4.0)	3.0 (1.9-3.3)	0.061
- Depression / self-perception	3.8 (3.2-4.4)	4.0 (3.4-4.4)	3.7 (2.3-4.4)	0.801
- Embarrassment	3.7 (2.9-4.0)	3.8 (3.2-4.0)	3.5 (2.6-4.0)	0.327
- Total score	14.3 (10.7-15.7)	15.8 (12.7-16.4)	13.5 (8.5-15.5)	0.167

Values are given as median (inter quartile range).

Males versus females

Figure 1 and 2 demonstrate the subanalyses of males (n=53) and females (n=26). Wexner and (subscale) FIQoL scores were comparable for males and females ($p > 0.500$; data not shown). Wexner scores were higher in elderly females compared with elderly males, indicating a worse degree of incontinence, but this was not significant ($p = 0.086$). There was a significant difference in scores for coping/behavior ($p = 0.010$) and depression/self-perception ($p = 0.036$) with lower (worse) scores for elderly females compared with elderly males. The other FIQoL subscale scores were comparable between both groups. Elderly females had higher Wexner scores compared with younger females, but this was not significant $p = 0.096$. The FIQoL subscales coping/behavior and depression/self-perception were significantly worse in elderly females ($p = 0.043$ and $p = 0.004$, respectively). There was a trend to a worse score on the subscales lifestyle ($p = 0.072$) and embarrassment ($p = 0.090$). Younger and elderly males had comparable scores. Only younger males scored worse on the FIQoL subscale depression/self-perception compared with younger females ($p = 0.044$), which is in contrast with elderly males and females.

DISCUSSION

This study describes the quality of life in terms of fecal incontinency in elderly patients after rectal cancer surgery. It seemed that elderly female had significantly worse scores on two FIQoL subscales (coping/behaviour and depression/self-perception) compared with both younger females and elderly males.

First, it is known from the general literature that fecal incontinence occurs more frequently in females than in males.[16,17] The underlying mechanisms are broad and may

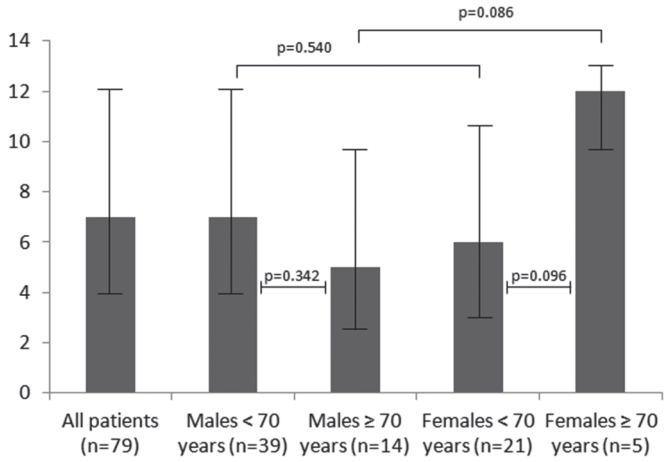
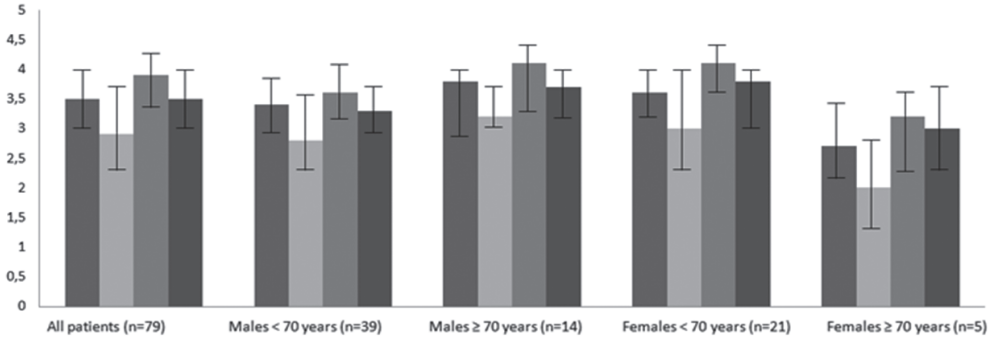


Figure 1. Wexner scores in male and female patients < or ≥ 70 years. A higher score indicates a worse outcome.



FIQoL scores (p-values)	*Female ≥70 vs male ≥70*	*Female ≥70 vs female <70*	*Male ≥70 vs male <70*	*Female <70 vs male <70*
Lifestyle	0.088	0.072	0.304	0.446
Coping / behavior	0.010*	0.043*	0.070	0.421
Depression / self-perception	0.036*	0.004*	0.073	0.044*
Embarrassment	0.130	0.090	0.172	0.105
Total scores	0.068	0.030*	0.090	0.184

Figure 2. FIQoL subscale scores in male and female patients < or ≥ 70 years with p-values. * significant p-values (p < 0.050). A lower score indicates a worse outcome.

include traumatic injuries to the anal sphincter complex, pelvic floor denervation due to vaginal deliveries, but also estrogen receptors in the anal sphincter and animal studies have shown an involution of the musculus levator ani during menarche.[17] Especially post-partum fecal incontinence is a frequently encountered problem after vaginal delivery and anal sphincter laceration.[18,19]

Second, apart from the female gender as predisposing factor for fecal incontinence, age-related changes in function of the anal sphincter may play an important role. Several studies showed a thickened external and internal anal sphincter with a decrease in sphincter pressure in elderly.[1,20] Furthermore, elderly females showed to have a reduced rectal compliance and sensation compared with younger females.[20] The median age of the patients in our group was 63 years. Due to the relatively small patient group, a cut-off point of 70 years was taken to define 'the elderly patient'. Despite this cut-off point, females with an increased age scored significantly worse on the FIQoL subscores.

Finally, iatrogenic anal sphincter damage and the creation of a neorectum (as during rectal cancer surgery) changes pelvic anatomy resulting in an altered diminished anal function with an increased risk of an anterior resection syndrome.[8] Also, it has been suggested that neoadjuvant therapy may affect anorectal function, but literature is controversial and limited.[8]

Treatment modalities for fecal incontinence after rectal surgery primary consist of dietary regimes and constipation agents. Also colonic irrigation has been described to reduce symptoms and improve quality of life.[21] Biofeedback training may be an alternative if these treatments fail, which includes training of the external sphincter contractility and physiotherapy of the pelvic floor muscles.[21] Limited studies have shown improvement of the degree of fecal incontinence after biofeedback training.[22] A more recent developed treatment is sacral nerve stimulation, in which a permanent pacemaker and electrode are placed, to stimulate the sensory, motoric and autonomic nerves of the sacral roots.[23]

The Wexner score did not significantly differ between younger patients and elderly, in contrast to the FIQoL subscale scores. The Wexner score includes only questions on the type of incontinence but not quality of life. A few years ago the LARS score was developed, which is a score based on the impact of the low anterior resection syndrome on quality of life.[24,25]

As different treatment options have been introduced during the last years to improve sphincter function and reduce fecal incontinence, the main question how to treat the elderly (female) still remains. A good cognition, cooperation, mobility and a low comorbidity status are required for a more successful outcome of these treatment options in the reduction of fecal incontinence, but elderly are usually not the most optimal patient group for most of these treatments. This further raises the question whether or not to perform sphincter-preserving rectal cancer surgery.

Limitation of this study was its retrospective character. Questionnaires were conducted months after surgery and there was no information on quality of life prior to surgery. Patients in whom bowel continuity was not restored at time of this study were excluded. Also, a large group was excluded due to mortality, loss-to-follow up, unresponsiveness or no permission for inclusion, which may also introduce selection bias. Furthermore, the obstetric history of the females was missing in the database. However, despite this small group of patients, significant differences were seen between patient groups. Large observational cohort studies are necessary to identify risk factors and to determine the role of EUS or physiotherapy.

In conclusion, elderly females have a decreased quality of life in terms of coping/behavior and depression/self-perception due to fecal incontinency following rectal cancer surgery. The elderly female patient (taken the obstetric history into account) should specifically be informed about the impact related to quality of life and the risk of an anterior resection syndrome and this should not be underestimated by clinicians and patients. The creation of a definite stoma or not to restore bowel continuity should therefore be strongly considered in this patient group.

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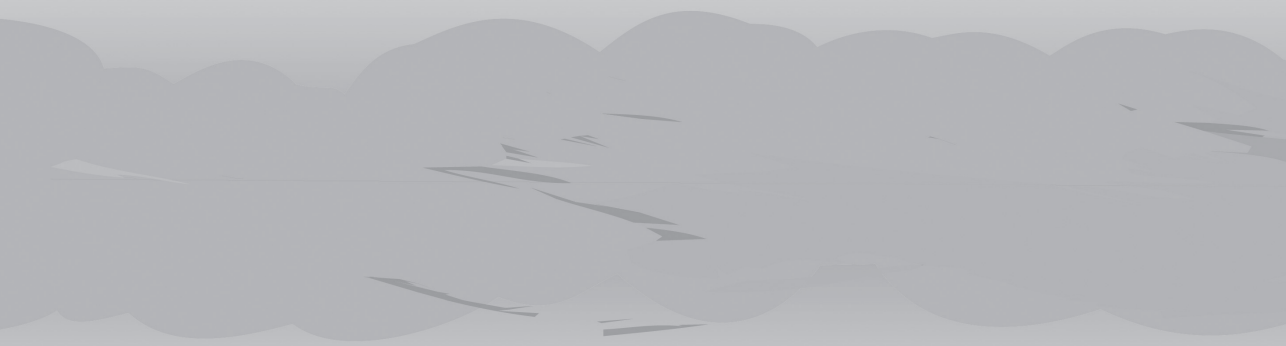


Chapter 11

Summary and future perspectives

SUMMARY

As stated in the introduction (***Chapter 1***), colorectal cancer is an important health issue, and colorectal surgery is increasingly being performed. During the last years, quality and safety of care, new surgical techniques and attention for peri-operative risks resulted in reduction of postoperative morbidity and mortality. Despite these improvements, complications still occur.

The aim of this thesis was to gain more insight in optimization of peri-operative care in colorectal surgery. Four main subjects were discussed in the presented chapters:

1. Analyzing peri-operative risk factors for complications following colorectal surgery.
2. Assessing the value and visualization of the visceral microcirculation in colorectal surgery.
3. Early detection of complications following colorectal surgery.
4. Functional outcomes and the impact on quality of life following colorectal surgery.

Part 1. Risk factors and complications after colorectal surgery

Over the years, surgical techniques have been optimized to reduce the risks of postoperative complications. In ***Chapter 2***, a laparoscopic technique of creating a fully intracorporeal anastomosis during right hemicolectomy is performed. Previous studies have been proven that laparoscopic colorectal surgery has been preferred above 'open' abdominal surgery in terms of shorter hospital stay, earlier return to work, less delayed gastric emptying or postoperative ileus and cardiopulmonary complications. When creating an intracorporeal anastomosis, externalization of vital bowel is no longer necessary. Traction on the bowel may therefore be diminished. Cosmesis may be improved, since incisions may be small. We investigated this procedure in 162 oncological patients. An R0-resection was achieved in 100%. The anastomotic leakage rate was 3.1%. The local recurrence rate was 0.8% with a two-year survival of 85.4%. We concluded that this procedure is technically and oncologically safe.

The elderly are an increasingly important patient group in colorectal surgery, but this is also a challenging patient group. Besides the colorectal malignancy, elderly have commonly significant other comorbidities, which increase the surgical risks. In ***Chapter 3***, we analyzed the early postoperative course on the outcome at one year. The early mortality rate was 6.3%. Of all survivors of primary surgery, another 9.9% of the patients died during the first year post surgery. Postoperative complications occurred in 46.2%. Reoperations were necessary in 17.0%. A total of 4.5% were admitted to the ICU for more than five days and 13.5%

was readmitted to the hospital. In the multivariate analysis, a higher ASA score, stage IV disease and postoperative complications were independently associated with a worse one year outcome. Reoperations, readmissions and ICU stay were not associated with one year survival. In conclusion, peri-operative care should be optimized in elderly patients by early identification of patients at risk for adverse events in a multidisciplinary approach.

Part 2. Visceral circulation and colorectal surgery

Many factors contribute to an adequate healing of the bowel anastomosis. One major criteria is an optimal vascular supply and tissue oxygenation.

First, we investigated in ***Chapter 4*** whether visceral vascular damage, in terms of atherosclerosis, was related to anastomotic failure. The pre-operative CT scans of 242 patients were reviewed by two radiologists, and the grade of stenosis and nature of the plaque in the celiac trunk, superior and inferior mesenteric arteries and iliac arteries was determined. In almost 60% of the patients, no clinically relevant vascular damage was observed. Over 40% had a stenosis of more than 50% in more than one visceral artery, almost 20% of the patients in more than two arteries and about 10% in more than three arteries. About 9% suffered from a total occlusion of the artery in more than one artery. There were no differences in the degree of vascular damage between patients with or without anastomotic leakage. Not even when analyzed for vascular supply and resection according to the anatomy (i.e. supply of inferior mesenteric artery and left-sided colorectal resections). We concluded that higher degrees of vascular damage were not resulting in more leakage in patients with chronic compromised vascular supply. There is no indication for prior routinely visualization of the visceral circulation or radiological intervention if vascular supply may seemed compromised in these patients.

Second, in ***Chapter 5***, we look further to the microvascular supply of the bowel. We present a technique in which the microcirculation of a human serosal bowel is visualized for the first time during surgery by using sidestream darkfield imaging. SDF is a technique in which polarized light is used to visualize erythrocytes through capillaries. A total of 52 representative measurements in seventeen patients were performed. Bowel images were compared to sublingual measurement and outcomes were comparable. Therefore, this imaging technique seems promising.

Part 3. Early detection of postoperative complications after colorectal surgery

As previously mentioned, anastomotic leakage is a severe complication with high morbidity and mortality rates. To reduce these rates, early detection is of importance. Besides

medical history and physical examination of the patient, the preferred additional imaging is abdominal CT scanning in the diagnosis of anastomotic leakage. In order to determine the value of CT scanning in the detection of anastomotic leakage, the literature is reviewed in ***Chapter 6***. Eight studies, including 221 abdominal CT scans, were included. The overall sensitivity was 0.68 (95% confidence interval 0.59-0.75) for colonic resection. Limitations of this review were the poor quality of the available studies, and wide variation in the definition of anastomotic leakage among the studies. Furthermore, there was no data on the sequelae of a false-negative CT scan outcome. As a result, we performed a study in 524 patients who underwent colorectal surgery and analyzed 97 postoperative CT scans of the patients who were suspected for anastomotic leakage. In addition, we analyzed the consequences of false positive and negative CT outcomes. The results of this study are described in ***Chapter 7***. The overall sensitivity of CT scanning in the detection of anastomotic leakage after colorectal surgery was comparable with the results in the review: 0.59 (95% CI 0.43-0.73). The specificity was 0.88 (95% CI 0.75-0.95), the positive predictive value 0.82 (95% CI 0.64-0.92), the negative predictive value 0.70 (95% CI 0.57-0.81), with an accuracy of 74%. The mortality rate following a delay in adequate diagnosing and treatment of anastomotic leakage due to a false negative CT outcome was 62.5%. The key message of this study is the alertness on clinical deterioration in combination with a 'negative CT scan'. Reassessment in these patients is important to decrease delay in diagnosis and treatment.

To adequately respond on postoperative complications following colorectal surgery, especially anastomotic leakage, an optimal clinical diagnostic strategy is necessary. In outspoken cases, the diagnosis can be easily made, but when symptoms are subtle, diagnosing of clinically important morbidity may be delayed. In ***Chapter 8***, a study protocol of the multicenter CONDOR-study (Early COmplication Detection after colORectal surgery) is presented. The aim of the CONDOR study is to develop an optimal diagnostic algorithm to early identify patients with anastomotic leakage after colorectal surgery. The study focuses on the evaluation of each step during the postoperative course and estimates the value of different clinical and radiological parameters.

Part 4. Functional outcome and quality of life after colorectal surgery

A less discussed topic in colorectal surgery is the quality of life in terms of fecal incontinence. Sphincter preserving surgery is supposed to have a better quality of life compared with abdominoperineal resection with a definitive stoma. In ***Chapter 9*** the predicting factors for fecal incontinence and related quality of life following sphincter preserving surgery for the treatment of rectal cancer are investigated. The validated Wexner and FIQoL scores (to analyze the degree of incontinence and related quality of life) were obtained from 80 patients. A diverting ileostoma was an independent predictor of a worse

FIQoL coping/behavior score. Furthermore, stoma reversal within 3 months after surgery showed better outcomes on Wexner and FIQoL scores compared with reversal after 3 months. Patients should be informed on these results and the choice whether or not to preserve the sphincter or to reverse the stoma should be discussed with the patient.

With aging, the anal sphincter function changes and fecal incontinence is a major concern. Since more elderly are undergoing rectal cancer surgery, this issue to preserve sphincter function in elderly becomes more important. In ***Chapter 10***, the difference between elderly patients and younger patients in quality of life, in terms of fecal incontinence, following rectal were analyzed. The main results of this study are that elderly and younger patients had comparable Wexner and FIQoL scores, but elderly females had significantly worse FIQoL subscale scores compared with younger females or elderly males. Elderly and younger males had comparable results. It should be strongly considered not to preserve sphincter function in elderly females to prevent decrease in quality of life due to fecal incontinence.

FUTURE PERSPECTIVES

The eventual goal is the reduction of the peri-operative risks in colorectal surgical care and improvement of the outcomes. One of the main steps in risk reduction is the identification of the current peri-operative care and the pitfalls associated with it. During the years, new techniques, improvement of health care and safety programs, earlier identification of patients at risk and multidisciplinary approaches have been introduced and have shown their effectiveness. However, we have not only to focus on general risks in the general population, but we have to more individualize peri-operative patient management. Risks for each patient need preoperatively to be clarified, and focus may be on prevention of complications by early identification and management.

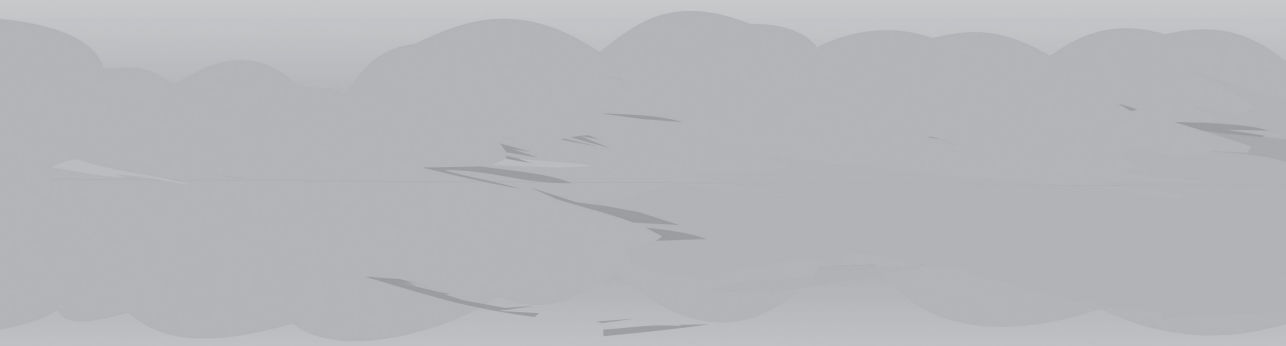
With the findings in this thesis, we are a step closer to patient-tailored medicine. In the first part, it is shown that renewal in surgical techniques, i.e. the creation of an intracorporeal anastomosis may have advantages. Introduction of this technique may improve the outcomes in patients undergoing right hemicolectomy. Furthermore, elderly patients with more comorbidities, a higher stage disease and postoperative complications seemed to have a more poor outcome. However, when surviving a prolonged ICU stay as a result of complications, one year outcome is reasonable. Responding to these comorbidities, may provide better management of postoperative, mostly non-surgical, complications and hopefully better outcomes. In the last part of the thesis, a relative less known topic,

on the impact of fecal incontinency on quality of life, is discussed. Results of these two studies are important and this should not be underestimated by the clinicians and the patients. Detailed discussions with the patients should result in a tailored-made choice for a surgical technique.

The second part of the thesis focuses on the value of the visceral circulation and microcirculation. It was shown that atherosclerosis of the visceral arteries was not associated with anastomotic leakage. Besides management of atherosclerosis to reduce the general risks of atherosclerosis, it is not recommended to improve visceral supply by treatment with percutaneous transluminal angioplasty. More interesting is the introduction of the sidestream dark field imaging technique, in which the microvascular circulation of the serosal bowel can be visualized. In a pilot study we proved the applicability of the technique. Future studies may provide more information in understanding and assessment of anastomotic healing. The final goal is the use of SDF in determine the exact position of the anastomosis, to create a most optimal well vascularized anastomosis.

The third part focuses on early identification of postoperative complications, especially anastomotic leakage. We have demonstrated that the sensitivity of abdominal CT-scanning in the detection of anastomotic leakage is relatively low. For now, CT-scanning is the preferred radiological image in the detection of anastomotic leakage. The key message of the studies is to interpret the CT outcome with caution, and relate the outcome with the clinical course of the patient. With the introduction of the CONDOR-study, an optimal diagnostic algorithm (with the combination of clinical history, physical examination, laboratory results, and additional radiological imaging) to early identify patients with anastomotic leakage after colorectal surgery will be created. With this algorithm, surgeons and residents will be triggered to early identify patients with a deteriorating clinical course. This will improve the quality and safety of care with better outcomes.

In summary, so fare we are doing well and peri-operative care has already been improved. Now we have to focus on patient-tailored medicine. The future lies in individualized care of colorectal patients. From the moment of diagnosing and indication to provide the surgery, the pathway of the colorectal patient should include: 1. Identification of the patients' risk followed by an optimal preoperative management of risk factors (disciplinary); 2. The use of optimal surgical techniques and to perform surgery on the base of patient-tailored medicine; 3. Postoperative management of risk factors and to make sure to early identify complications if these may occur with the main goal to improve the outcome of the individual patient.



Chapter 12

Samenvatting en toekomstperspectieven

SAMENVATTING

Zoals in de introductie (***Hoofdstuk 1***) al genoemd werd is darmkanker een belangrijk gezondheidsprobleem, en worden darmoperaties hiervoor steeds vaker uitgevoerd. Gedurende de laatste jaren hebben de kwaliteit en veiligheid van de zorg, nieuwe chirurgische technieken en aandacht voor peri-operatieve risico's geleid tot een reductie van de postoperatieve morbiditeit en mortaliteit. Helaas treden ondanks deze verbeteringen nog steeds complicaties op.

Het belangrijkste doel van dit proefschrift is meer inzicht te verkrijgen in de optimalisatie van de peri-operatieve zorg in de colorectale chirurgie. De vier belangrijkste onderwerpen worden in de verschillende hoofdstukken besproken en zijn:

1. Het analyseren van peri-operatieve risicofactoren voor complicaties na colorectale chirurgie.
2. De waarde bepalen van de viscerale microcirculatie voor de colorectale chirurgie en het in beeld brengen ervan.
3. Vroege detectie van complicaties na colorectale chirurgie.
4. De functionele uitkomst en de impact op de kwaliteit van leven na colorectale chirurgie bepalen.

Deel 1. Risicofactoren en complicaties na colorectale chirurgie

Gedurende de jaren zijn de chirurgische technieken verbeterd om de risico's op postoperatieve complicaties te verkleinen. In ***Hoofdstuk 2*** wordt een laparoscopische techniek beschreven om een darmanastomose in het lichaam te maken tijdens de hemicolectomie rechts. Eerdere studies hebben laten zien dat laparoscopische colorectale chirurgie een voorkeur heeft boven de 'open' abdominale chirurgie met een kortere ziekenhuis opnameduur, sneller hervatten van de werkzaamheden, minder klachten van een postoperatieve gastroparese of ileus en minder cardiopulmonale complicaties. Wanneer er een intracorporele anastomose gemaakt wordt, hoeft de vitale darm niet buiten het lichaam gebracht te worden. Hierdoor ontstaat er minder tractie op de darm. De cosmetiek zal hierdoor verbeterd worden omdat er een minder grote incisie nodig is. Deze procedure werd in 162 oncologische patiënten onderzocht. Er werd in alle patiënten een R0-resectie verkregen. Het naadlekkage percentage was 3.1%. Het lokaal recidief trad in 0.8% op en de twee-jaars overleving was 85.4%. Onze conclusie was hierdoor dat deze procedure technisch en oncologisch veilig is.

Ouderen patiënten zijn een steeds belangrijkere groep patiënten binnen de colorectale chirurgie, maar vormen tegelijk ook een uitdagende patiënt groep. Naast darmkanker, hebben deze ouderen vaak ook significante andere comorbiditeiten, die het operatie risico vergroten. In ***Hoofdstuk 3*** bekijken we het effect van het vroege postoperatieve beloop op de uitkomst een jaar na de operatie. De vroege mortaliteit was 6.3%. Van alle patiënten die de operatie overleefd hebben, overleden nog eens 9.9% gedurende het eerste jaar. Postoperatieve complicaties traden op in 46.2%. Reoperaties waren nodig in 17.0%. Totaal 4.5% werd opgenomen op de intensive care voor langer dan 5 dagen en 13.5% werd heropgenomen in het ziekenhuis. In de multivariate analyse bleken stadium IV ziekte, postoperatieve complicaties en een hogere ASA score onafhankelijk geassocieerd met een slechtere één-jaars uitkomst. Reoperaties, heropnames en IC-opnames bleken geen effect te hebben op de één-jaars overleving. Concluderend, multidisciplinaire zorg kan bijdragen aan vroegere identificatie van risicopatiënten en een verbetering van de peri-operatieve zorg in oudere patiënten.

Deel 2. De viscerale circulatie en colorectale chirurgie

Veel factoren dragen bij aan een adequate genezing van de darm anastomose. Een belangrijk criterium hierbij is een optimale bloedvoorziening en weefsel oxygenatie.

We hebben eerst in ***Hoofdstuk 4*** gekeken of viscerale vaatschade, zoals atherosclerose, gerelateerd was aan het falen van de anastomose. Hiervoor zijn 242 pre-operatieve CT-scans beoordeeld door twee radiologen, en werd de ernst van de stenose en het type plaque in de truncus coeliacus, de arterie mesenterica superior en inferior en de iliacaal vaten bepaald. In bijna 60% van de patiënten werd er geen klinisch relevante vaatschade gedetecteerd. Meer dan 40% had een stenose van ruim 50% in meer dan één visceraal bloedvat, bijna 20% had deze afwijking in meer dan twee bloedvaten, en ongeveer 10% zelfs in meer dan drie bloedvaten. Rond de 9% had een totale occlusie van meer dan één arterie. Er werden geen verschillen gevonden in de ernst van de vaatschade ten opzichte van de naadlekkages. Dit werd ook niet gevonden wanneer gekeken werd naar schade in de bloedtoevoer van de gereseceerde darm (zoals voorziening van de arterie mesenterica inferor bij een links-zijdige colectomie). We concludeerden daarom ook dat meer vaatschade niet lijdt tot meer naadlekkages bij patiënten met al een chronisch gecompromitteerde circulatie. Er is dus geen indicatie voor routinematige visualisatie van de viscerale circulatie of radiologische interventie als de bloedtoevoer gecompromitteerd blijkt in deze patiënten.

Als tweede hebben we in ***Hoofdstuk 5*** verder gekeken naar de microvascularisatie van de darm. We hebben een techniek gepresenteerd waarin de microvascularisatie van de

humane serosale darm voor het eerst zichtbaar is gemaakt met "Sidestream darkfield (SDF) imaging" gedurende de operatie. SDF is een techniek waarbij gepolariseerd licht gebruikt wordt om erythrocyten door de capillairen te visualiseren. Er werden totaal 52 metingen verricht bij 17 patiënten. De beelden van de darm werden vergeleken met de sublinguale metingen, waarbij de resultaten vergelijkbaar waren. Deze techniek lijkt dus veel belovend.

Deel 3. Vroege detectie van postoperatieve complicaties na colorectale chirurgie

Zoals eerder al genoemd werd, is naadlekkage een zeer ernstige complicatie met een hoge morbiditeit en mortaliteit. Om dit te reduceren is vroege detectie van belang. Naast anamnese en lichamelijk onderzoek, wordt veel gebruik gemaakt van de CT-scan om de naadlekkage op te sporen. Om de waarde van deze CT-scan voor het diagnosticeren van de naadlekkage te bepalen, werd een literatuur onderzoek verricht en verwerkt in een review welke beschreven wordt in ***Hoofdstuk 6***. Totaal werden acht studies met 221 abdominale CT-scan geïncludeerd. De overall sensitiviteit was 0.68 met een 95% betrouwbaarheids interval van 0.59-0.75 voor colon resecties. Beperkingen van deze review waren de matige kwaliteit van de beschikbare studies en een grote spreiding in de definitie van de naadlekkage. Daarnaast was er geen informatie beschikbaar over de consequenties van een vals-negatieve CT-scan uitslag. Vervolgens hebben wij een studie verricht in 524 patiënten die een colorectale operatie hebben ondergaan en hebben we 97 CT-scan bekeken van de patiënten die verdacht werden van een naadlekkage. Daarnaast hebben we ook naar de consequenties gekeken van een vals-positieve en vals-negatieve CT-scan uitslag. De resultaten van deze studie zijn beschreven in ***Hoofdstuk 7***. De overall sensitiviteit van de CT-scan op verdenking naadlekkage na een colorectale operatie was vergelijkbaar met de sensitiviteit van de review: 0.59 (0.43-0.73). De specificiteit was 0.88 (0.75-0.95), de positief voorspellende waarde was 0.82 (0.64-0.92), de negatief voorspellende waarde was 0.70 (0.57-0.81), met een accuratesse van 74%. De mortaliteit na een vertraging in de juiste diagnose en behandeling van de naadlekkage ten gevolge van een negatieve CT-scan uitslag was 62.5%. De belangrijkste boodschap van deze studie is de alertheid op klinische verslechtering in combinatie met een 'negatieve CT-scan uitslag'. Geregelde herbeoordeling in deze patiënten is dus van belang om vertraging in diagnose en behandeling te voorkomen.

Om goed te kunnen reageren op postoperatieve complicaties na colorectale chirurgie, vooral naadlekkages, is een optimale klinisch diagnostische strategie nodig. In duidelijke gevallen kan de diagnose makkelijk gesteld worden, maar als symptomen meer subtiel zijn kan het diagnosticeren van belangrijke morbiditeit vertraagd worden. In ***Hoofdstuk 8***

wordt het studie protocol van de CONDOR studie ("vroege detectie van complicaties na colorectale chirurgie") besproken. Het doel van de CONDOR studie is een optimaal diagnostisch algoritme ontwikkelen om patiënten met bijvoorbeeld een naadlekkage na colorectale chirurgie sneller te identificeren. De studie focust zich op de evaluatie van elke stap in het postoperatieve beloop en bepaalt de waarde van verschillende klinische en radiologische parameters.

Deel 4. Functionele uitkomst en kwaliteit van leven na colorectale chirurgie.
Een minder bediscussieerd onderwerp in de colorectale chirurgie is de kwaliteit van leven op basis van fecale incontinentie. Sfincter-sparende chirurgie zou voor een betere kwaliteit van leven zorgen vergeleken met de abdomino-perineale resectie waarbij een definitief stoma aangelegd wordt. In ***Hoofdstuk 9*** worden de voorspellende factoren voor fecale incontinentie en de gerelateerde kwaliteit van leven na sfincter-sparende operaties voor rectum kanker onderzocht. De gevalideerde Wexner en FIQoL scores (om de mate van ernst van incontinentie en kwaliteit van leven te beoordelen) werden verzameld van 80 patiënten. Een diverterend ileostoma was een onafhankelijke voorspeller van een slechtere FIQoL coping/gedrag score. Daarnaast bleek het opheffen van het stoma binnen 3 maanden na de primaire operatie betere uitkomsten van de Wexner en FIQoL scores te hebben vergeleken met de scores van patiënten waarbij het stoma pas na 3 maanden opgeheven werd. Patiënten moeten beter op de hoogte gebracht worden van deze resultaten en samen moet besproken worden of de sfincter behouden moet blijven of dat het stoma wel of niet opgeheven moet worden.

Bij het ouder worden gaat de sfincter functie achteruit en wordt fecale incontinentie een steeds groter probleem. Steeds meer ouderen ondergaan rectum chirurgie voor rectum kanker, waardoor de discussie of de sfincter bij ouderen wel of niet behouden moet blijven, steeds belangrijker wordt. In ***Hoofdstuk 10*** worden de verschillen in kwaliteit van leven door fecale incontinentie tussen ouderen en jongere patiënten na rectum chirurgie bekeken. De belangrijkste resultaten van deze studie laten zien dat ouderen en jongeren vergelijkbare Wexner en FIQoL scores hebben, maar dat oudere vrouwen een significant slechtere FIQoL score hebben vergeleken met jongere vrouwen of oudere mannen. Oudere en jongere mannen hebben vergelijkbare resultaten. Het moet dan ook sterk overwogen worden om de sfincter functie in oudere vrouwen niet te behouden tijdens de operatie, zodat de kwaliteit van leven niet verlaagd wordt door fecale incontinentie.

TOEKOMSTPERSPECTIEVEN

Het uiteindelijke doel is het reduceren van de peri-operatieve risico's in de colorectaal chirurgische zorg en een verbetering van de uitkomsten. Een van de belangrijkste stappen in risico reductie is het identificeren van de huidige peri-operatieve zorg en de valkuilen hierin. Gedurende de afgelopen jaren zijn er nieuwe technieken geïntroduceerd, zijn de gezondheidszorg en veiligheid verbeterd, worden patiënten met een risico vroeger geïdentificeerd en worden patiënten multi-disciplinair besproken, en allen met een goed effect. Echter, we moeten niet alleen focussen op algemene risico's van de algemene populatie, maar we moeten naar een meer geïndividualiseerde peri-operatieve patiënten zorg toe. Risico's moeten preoperatief voor elke patiënt al duidelijk zijn, en het focus moet liggen op preventie van complicaties door vroegere identificatie en behandeling.

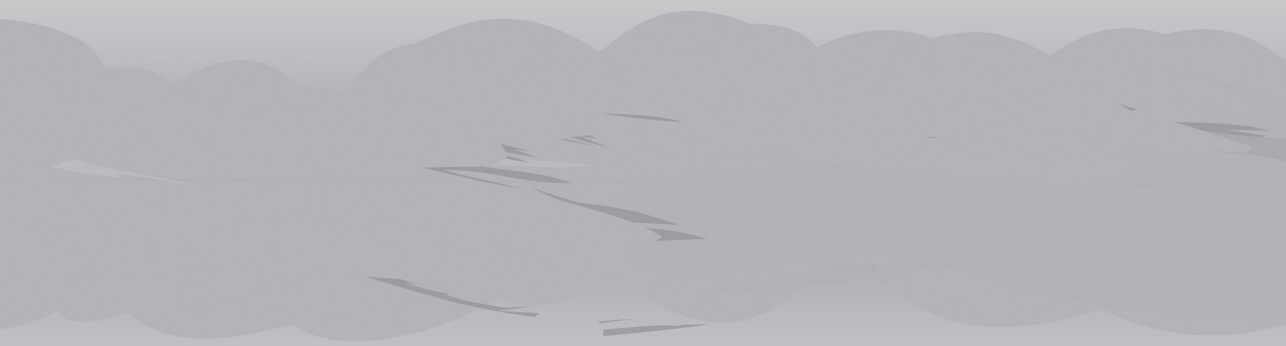
Met de bevindingen in dit proefschrift, zijn we al een stap dichterbij de voor de patiënt op maat gemaakte zorg. In het eerste deel laten we zien dat een nieuwe chirurgische techniek, het maken van een intracorporele anastomose, voordelen heeft. Het introduceren van deze techniek zou de uitkomsten van de patiënt die een hemicolectomie rechts ondergaat kunnen verbeteren. Daarnaast laten we zien dat oudere patiënten met meer comorbiditeit, een hoger ziekte stadium en postoperatieve complicaties een slechtere uitkomst hebben. Echter, als ze een langdurige IC-opname overleven, hebben ze een goede één-jaars overleving. Eerder identificeren van deze comorbiditeiten kan zorgen voor een betere postoperatieve behandeling van, meestal niet-chirurgische, complicaties en hopelijk zorgen voor een betere uitkomst. In het laatste deel van het proefschrift wordt iets dieper ingegaan op een relatief onderbelicht onderwerp, namelijk de impact van fecale incontincentie op de kwaliteit van leven. Resultaten van deze twee studies zijn belangrijk en laten zien dat dit niet onderschat moet worden. Een uitvoerig gesprek met de patiënt moet dan ook zorgen voor een passende operatie bij de juist patiënt.

In het tweede deel van het proefschrift ligt de focus op de viscerale circulatie en microcirculatie. Atherosclerose van de viscerale vaten leek geen effect te hebben op het ontstaan van naadlekkages. Naast het behandelen van atherosclerose tegen de algemene risico's wordt het niet aanbevolen om de viscerale circulatie te verbeteren door b.v. een percutane transluminale angioplastiek. Interessanter is de introductie van de 'sidestream darkfield imaging' techniek, waarbij de microcirculatie van de serosa van de darm in beeld gebracht kan worden. In deze pilot studie hebben we laten zien dat dit een haalbare techniek is. Toekomstige studies zouden ons meer informatie kunnen geven om de genezing van een darm anastomose beter te begrijpen. Het uiteindelijke doel is het gebruik van SDF om de

exacte positie van de naad te bepalen, om een optimaal gevascularisseerde naad aan te leggen.

Het derde deel van het proefschrift focust op vroege identificatie van postoperatieve complicaties, en met name naadlekkage. We hebben laten zien dat de sensitiviteit van de abdominale CT-scan bij een verdenking op een naadlekkage relatief laag is. Tot nu toe is de CT-scan het diagnostisch middel van voorkeur. De boodschap is echter dat de uitslag van de CT-scan met zorg geïnterpreteerd dient te worden, en dat de uitkomst altijd gerelateerd moet zijn aan de kliniek van de patiënt. Met het starten van de CONDOR-studie hopen we een optimaal diagnostisch algoritme te ontwikkelen met de combinatie van anamnese, lichamelijk onderzoek, laboratorium onderzoek en aanvullende radiologische onderzoeken, om patiënten met een naadlekkage na colorectale chirurgie eerder te identificeren. Hiermee worden chirurgen en arts-assistenten ook getriggerd om patiënten met een verslechtering in kliniek eerder te herkennen. Dit zal de kwaliteit en veiligheid van de zorg verbeteren.

Samenvattend zijn we al goed op weg en is de peri-operatieve zorg al duidelijk verbeterd. Nu moeten we meer focussen op de op-maat-gemaakte geneeskunde. De toekomst ligt in een geïndividualiseerde zorg voor colorectale patiënten. Vanaf het moment van de diagnose en de indicatie tot opereren moet het vervolg van de colorectale patiënt zijn: 1. Identificatie van risicofactoren gevolgd door een optimale preoperatieve zorg en verbetering van deze risico factoren (multidisciplinair); 2. Het gebruik van optimale chirurgische technieken en de juiste operatie voor de individuele patiënt; 3. Postoperatief inspelen op risicofactoren en het vroeger herkennen van de complicaties met als belangrijkste doel het verbeteren van de uitkomst voor de individuele patiënt.



Chapter 13

Appendices

CURRICULUM VITAE

Verena Kornmann werd geboren op 29 oktober 1984 in Arnhem, alwaar zij opgroeide met haar jongere zusje en broertje. Na het behalen van haar VWO diploma in 2003 besloot zij geneeskunde te willen studeren. Echter na uitgeloot te zijn voor de geneeskunde studie, startte ze de studie Biomedische Wetenschappen aan de Universiteit in Utrecht. Het jaar daarop werd ze wederom uitgeloot voor de geneeskunde studie, waarop zij besloot eerst haar bachelor Biomedische Wetenschappen te behalen in 2006. Na deze bachelor studie, werd zij in 2006 toegelaten tot masteropleiding Selective Utrecht Medical Master (SUMMA) aan de Universiteit van Utrecht. In augustus 2010 behaalde zij hiermee de graad Master of Science voor Geneeskunde en klinisch onderzoeker. Vanaf september 2011 was ze werkzaam als ANIOS chirurgie in het St. Antonius ziekenhuis te Nieuwegein. Hier werd ook de basis gelegd voor het promotie-onderzoek. Van maart 2012 tot februari 2013 was er de mogelijkheid tot full-time onderzoek vanuit het St. Antoniusziekenhuis. In deze periode zijn er diverse onderzoeken opgestart die bijgedragen hebben tot dit proefschrift. Daarnaast was ze onderzoeksbegeleidster van diverse co-assistenten en studenten, studie coordinator van twee andere studies (de Chocolate trial en de Peanuts trial) en was ze winnaar van het St. Antonius oncologie fonds. Hierna werkte ze gedurende enkele maanden als ANIOS chirurgie in het St. Antoniusziekenhuis en gedurende een half jaar als ANIOS chirurgie in het Universitair Medisch Centrum te Utrecht, om vervolgens per 1 januari 2014 toegelaten te worden tot de opleiding chirurgie in de regio Nijmegen. Momenteel werkt ze op de afdeling chirurgie onder leiding van Dr. S. Lemson in het Slingeland ziekenhuis te Doetinchem. In juli 2016 zal zij haar opleiding vervolgen in het Radboud Universitair Medisch Centrum te Nijmegen.

PhD PORTFOLIO

Name PhD student:	Verena Kornmann, MSc.
PhD period:	2012-2015
Promotor:	Prof. Dr. M. A. Boermeester
Co-promotores:	Dr. D. Boerma, Dr. B. van Ramshorst

PhD training

- *Course Scientific English writing and oral presentation* (2013), Babel, Nieuwegein
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- *Course RefWorks* (2013), Antonius Academy, Nieuwegein
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- *Course Scientific Poster Presentation* (2012), Antonius Academy, Nieuwegein
- *Internal Good Clinical Practice monitoring* (2012), St. Antonius hospital, Nieuwegein
- *Good Clinical Practice* (2012), Roche Netherlands BV and Antonius Academy, Nieuwegein

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- Presentation, local reference meeting, Slingeland hospital, Doetinchem (2014): *"Critical appraised topic: the value of the abdominal CT-scan in detecting anastomotic leakage".*
- Poster, NVvH autum congress, 's Hertogenbosch (2013): *"Sfincterfunctie en gerelateerde kwaliteit van leven na TME met primaire anastomose bij patiënten met een rectumcarcinoom"*.
- Presentation, NVvH annual Duth surgical congress, Veldhoven (2013): *"Hoge mortaliteit na een vals negatieve CT uitkomst voor naadlekkages na colon chirurgie".*
- Presentation, local reference meeting, department of surgery in 5 Dutch hospitals (2012-2013): *"De CHOCOLATE en de PEANUTS trial."*
- Presentation, grants winning studies, Antonius academy Nieuwegein (2012): *"Wat is de PEANUTS trial?"*
- Presentation, regional reference meeting Utrecht, St. Antoniushospital, Nieuwegein (2012): *"Valse geruststelling en vertraging diagnose naadlekkage door CT scans".*
- Presentation, 19th International Congress of the EAES, Turino, Italy (2011): *"Laparoscopic right hemicolectomy with intracorporeal anastomosis".*
- Presentation, NVvH annual Dutch surgical congress, Veldhoven (2011): *"Hemicolectomie rechts met intracorporele anastomose: een veilige methode?".*
- Poster, NVEC congress Leiden (2011): *"Laparoscopische hemicolectomie rechts met intracorporele anastomose: veilige methode?"*

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- Local reference meeting, St. Antoniushospital Nieuwegein (2011-2013), University Medical Center Utrecht (2013), Slingeland hospital Doetinchem (2014-2015).
- Regional reference meeting, region Utrecht (2011-2013) and region Nijmegen (2014-2015).
- NVvH Annual Dutch surgical congress, Veldhoven (2011-2015).
- NVvH autumn congress (2012-2014).
- International Hepato-Pancreato-Biliary Association (IHPBA) congress, Paris, France (2012).
- 19th International Congress of the European Association for Endoscopic Surgery (EAES), Turino, Italy (2011).
- Nederlandse Vereniging voor Endoscopische Chirurgie (NVEC), Leiden (2011).

Tutoring, mentoring

- Marieke Walma, master thesis (2012-2014): *"Functional outcome and related quality of life after low anterior resection for rectal cancer".*
- Nikki Treskes, bachelor thesis (2012-2013): *"The value of the abdominal CT-scan in the detection of anastomotic leakage after colorectal surgery".*
- Emma Wassenaar, 3 months science internship (2012): *"The effect of neo-adjuvant radiotherapy on anastomotic leakage after rectal resection".*
- Karin Hiemstra, 3 months science internship (2013): *"The role of a postoperative scoring system in early detection of anastomotic leakage after colorectal surgery".*

Grants, awards and prizes

Grant, oncology foundation, St. Antoniushospital, NIeuwegein (2013): *"The CONDOR study: Early COmplication Detection after colORectal surgery. A multicenter study."*

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Kornmann VNN, Vugt van JLA, Smits AB, Ramshorst van B, Boerma D. *The first year after colorectal surgery in the elderly.* Submitted.

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Geachte co-promotoren, dr. D. Boerma en dr. B. van Ramshorst.

Beste Djamila, tegelijk begonnen we in het St. Antonius. Jij als chirurg, ik als beginnende assistent. Enthousiast reagerend op de vraag of iemand de naadlekkages op een rij wilde zetten, had ik niet verwacht dat dit zou leiden tot een proefschrift. Niet alleen tijdens het onderzoek, maar ook in de kliniek en tijdens de weg naar de opleiding tot chirurg, heb je me overal gesteund. Ik ben je heel dankbaar hiervoor. Zonder jou was dit proefschrift er niet geweest.

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